



# ***STIC Search Report***

## **Biotech-Chem Library**

**STIC Database Tracking Number: 124713**

**TO: Shailendra Kumar**  
**Location: 5d61 / 5c18**  
**Tuesday, June 22, 2004**  
**Art Unit: 1621**  
**Phone: 272-0640**  
**Serial Number: 10 / 046622**

**From: Jan Delaval**  
**Location: Biotech-Chem Library**  
**Rem 1A51**  
**Phone: 272-2504**

**jan.delaval@uspto.gov**

### **Search Notes**

Jan please

Access DB# 104913

# SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: S. Kumar Examiner #: 64594 Date: 6/15/04  
 Art Unit: 1621 Phone Number 202-272-0640 Serial Number: 101046622  
 Mail Box and Bldg/Room Location: REM 5D61 Results Format Preferred (circle): PAPER DISK E-MAIL  
5C18

If more than one search is submitted, please prioritize searches in order of need.

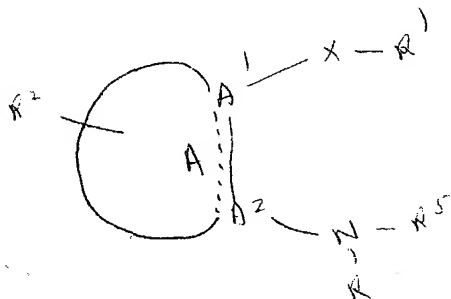
\*\*\*\*\*

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Substituted amine derivatives and methods of use  
 Inventors (please provide full names): Guoging Chen et al

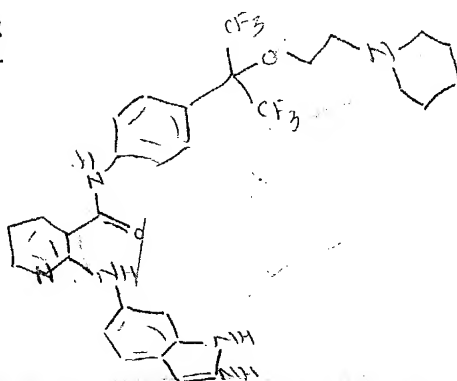
Earliest Priority Filing Date: 1/12/2001

\*For Sequence Searches Only\* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.



A is six membered heterocycle  
 X is 1  
 Z is 0 or 5  
 R is substituted 4-6 member heterocycle, aryl, bicyclic or tricyclic heterocycle.  
 R' is 6-10 member aryl, 4-6 heterocycle cycloalkyl etc.

Species



## STAFF USE ONLY

Searcher: [Signature]  
 Searcher Phone #: 22504  
 Searcher Location: \_\_\_\_\_  
 Date Searcher Picked Up: 6/21  
 Date Completed: 6/22  
 Searcher Prep & Review Time: \_\_\_\_\_  
 Clerical Prep Time: 30  
 Online Time: 1:20

## Type of Search

NA Sequence (#) \_\_\_\_\_  
 AA Sequence (#) \_\_\_\_\_  
 Structure (#) ☒ \_\_\_\_\_  
 Bibliographic \_\_\_\_\_  
 Litigation \_\_\_\_\_  
 Fulltext \_\_\_\_\_  
 Patent Family \_\_\_\_\_  
 Other \_\_\_\_\_

## Vendors and cost where applicable

STN ☒ \_\_\_\_\_  
 Dialog \_\_\_\_\_  
 Questel/Orbit \_\_\_\_\_  
 Dr.Link \_\_\_\_\_  
 Lexis/Nexis \_\_\_\_\_  
 Sequence Systems \_\_\_\_\_  
 WWW/Internet \_\_\_\_\_  
 Other (specify) \_\_\_\_\_

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 JUN 17 2004  
 1506

L Number	Hits	Search Text	DB	Time stamp
1	2200	(546/194,199).CCLS.	USPAT; US-PGPUB	2004/06/22 14:12
2	1249	(514/318).CCLS.	USPAT; US-PGPUB	2004/06/22 14:13

=> fil reg

FILE 'REGISTRY' ENTERED AT 07:26:10 ON 22 JUN 2004  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
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Property values tagged with IC are from the ZIC/VINITI data file  
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STRUCTURE FILE UPDATES: 21 JUN 2004 HIGHEST RN 697224-75-2  
DICTIONARY FILE UPDATES: 21 JUN 2004 HIGHEST RN 697224-75-2

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when  
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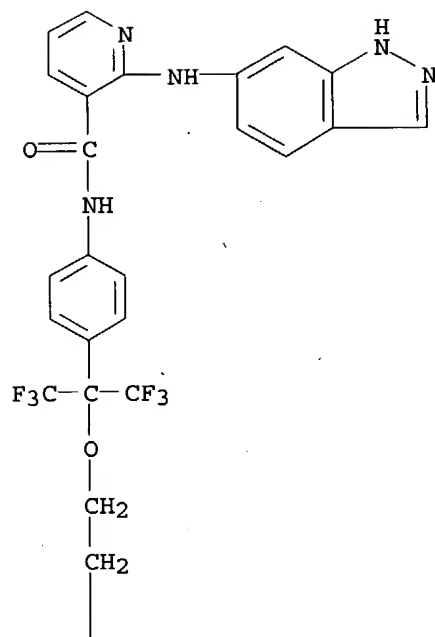
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more  
information enter HELP PROP at an arrow prompt in the file or refer  
to the file summary sheet on the web at:  
<http://www.cas.org/ONLINE/DBSS/registryss.html>

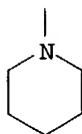
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L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN  
RN 454481-33-5 REGISTRY  
CN 3-Pyridinecarboxamide, 2-(1H-indazol-6-ylamino)-N-[4-[2,2,2-trifluoro-1-[2-(1-piperidinyl)ethoxy]-1-(trifluoromethyl)ethyl]phenyl]- (9CI) (CA INDEX NAME)  
FS 3D CONCORD  
MF C29 H28 F6 N6 O2  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL  
DT.CA Caplus document type: Patent  
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

PAGE 1-A



PAGE 2-A



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

2 REFERENCES IN FILE CA (1907 TO DATE)  
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:350636

REFERENCE 2: 137:216945

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SEL RN  
L3 0 S E1/CRN

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FILE 'HCAPLUS' ENTERED AT 07:25:41 ON 22 JUN 2004

L5 2 S L2

FILE 'USPATFULL, USPAT2' ENTERED AT 07:25:50 ON 22 JUN 2004

L6 2 S L2

FILE 'HCAPLUS, USPATFULL' ENTERED AT 07:25:57 ON 22 JUN 2004

L7 3 DUP REM L5 L6 (1 DUPLICATE REMOVED)

FILE 'REGISTRY' ENTERED AT 07:26:10 ON 22 JUN 2004

=> fil hcaplus uspatall

FILE 'HCAPLUS' ENTERED AT 07:26:18 ON 22 JUN 2004

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FILE 'USPAT2' ENTERED AT 07:26:18 ON 22 JUN 2004

CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

=> d l7 bib abs hitstr tot

L7 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1

AN 2003:855655 HCAPLUS

DN 139:350636

TI Preparation of amino heteroaryl amides for use in pharmaceutical compositions for the treatment of angiogenesis mediated diseases such as cancer

IN Patel, Vinod F.; Askew, Benny; Booker, Shon; Chen, Guoqing; Dipietro, Lucian V.; Germain, Julie; Habgood, Gregory J.; Huang, Qi; Kim, Tae-seong; Li, Aiwen; Nishimura, Nobuko; Nomak, Rana; Riahi, Babak; Yuan, Chester Chenguang; Elbaum, Daniel

PA Amgen Inc., USA

SO U.S. Pat. Appl. Publ., 148 pp., Cont.-in-part of U.S. Ser. No. 46,622. CODEN: USXXCO

DT Patent

LA English

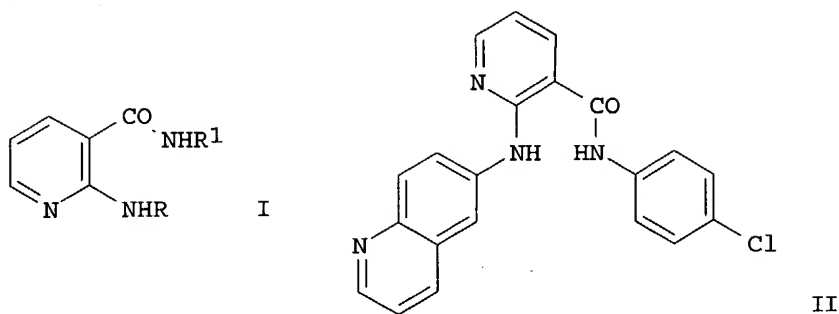
FAN.CNT 2

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PI	US 2003203922	A1	20031030	US 2002-197918	20020717
	US 2003195230	A1	20031016	US 2002-46622	20020110
	WO 2004007481	A2	20040122	WO 2003-US22275	20030715
	WO 2004007481	A3	20040219		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRAI	US 2001-261882P	P	20010112		
	US 2001-323808P	P	20010919		
	US 2002-46622	A2	20020110		

US 2002-197918 A 20020717

OS MARPAT 139:350636

GI



AB Amino substituted heteroaryl amides, such as I [R = nitrogen containing heteroaryl, such as quinolinyl, isoquinolinyl, indazolyl; R<sup>1</sup> = aryl, cycloalkyl, heteroaryl, heterocyclyl], were prepared for therapeutic use. The invention encompasses novel compds., analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compns. and methods for prophylaxis and treatment of cancer, angiogenesis related disorders, KDR-related disorders, cell proliferation related disorders, inflammation, reducing blood flow in tumors, reducing tumor size and diabetic retinopathy. Thus, amide II was prepared via an amination reaction of 2-chloronicotinic acid with 6-aminoquinoline followed by an amidation reaction of the aminonicotinic acid derivative thus formed with 4-chloroaniline. Biol. evaluations included HUVEC proliferation assay, inhibition of angiogenesis in the rat corneal neovascularization micropocket model, and antitumor activity using A431 rat tumor cells.

IT 454481-33-5P

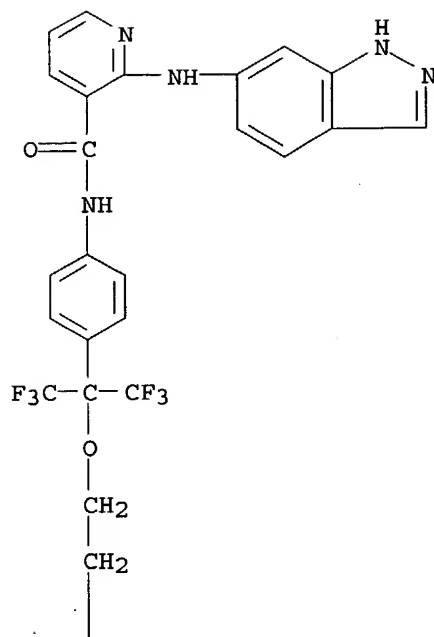
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of aminopyridinecarboxamides for therapeutic use in treatment of angiogenesis mediated diseases such as cancer)

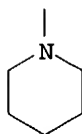
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CN 3-Pyridinecarboxamide, 2-(1H-indazol-6-ylamino)-N-[4-[2,2,2-trifluoro-1-[2-(1-piperidinyl)ethoxy]-1-(trifluoromethyl)ethyl]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



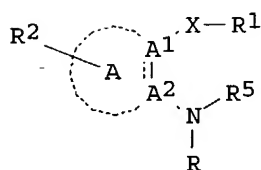
L7 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN  
 AN 2002:676007 HCAPLUS  
 DN 137:216945  
 TI Preparation of substituted 2-(1H-indazol-6-ylamino)nicotinamides for  
 treating KDR-related diseases  
 IN Chen, Guoqing; Adams, Jeffrey; Bemis, Jean; Croghan, Michael; Dipietro,  
 Lucian; Dominguez, Celia; Elbaum, Daniel; Germain, Julie; Huang, Qi; Kim,  
 Joseph L.; Ouyang, Xiaohu; Patel, Vinod F.; Smith, Leon M.; Tasker,  
 Andrew; Xi, Ning; Xu, Shimin; Yuan, Chester Chenguang; Kim, Tae-Seong  
 PA Amgen Inc., USA  
 SO PCT Int. Appl., 395 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002068406	A2	20020906	WO 2002-US3064	20020111
	WO 2002068406	A3	20030424		

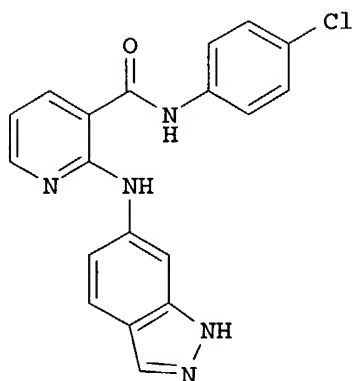
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 GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
 LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,

PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,  
 UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,  
 CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,  
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003195230 A1 20031016 US 2002-46622 20020110  
 EE 200300325 A 20031215 EE 2003-325 20020111  
 PRAI US 2001-261882P P 20010112  
 US 2001-323808P P 20010919  
 US 2002-46622 A 20020110  
 WO 2002-US3064 W 20020111  
 OS MARPAT 137:216945  
 GI



I



II

AB The title compds. [I; each of A<sub>1</sub> and A<sub>2</sub> = C, CH, N; A = 5-6 membered partially saturated heterocyclyl, 5-6 membered heteroaryl, 9-11 membered fused partially saturated heterocyclyl, etc.; X = C(:Z)N(R<sub>5a</sub>)R<sub>4</sub>; Z = O, S; R = (un)substituted 4-6 membered heterocyclyl, aryl, fused 9-14 membered bicyclic or tricyclic heterocyclyl; R<sub>1</sub> = (un)substituted 6-10 membered aryl, 4-6 membered heterocyclyl, cycloalkyl, etc.; R<sub>2</sub> = H, halo, cycloalkyl, etc.; R<sub>4</sub> = a bond, alkylene, alkenylene, etc.; R<sub>5</sub> = H, alkyl, (un)substituted Ph, aralkyl; R<sub>5a</sub> is not defined] which are effective for prophylaxis and treatment of diseases, such as angiogenesis mediated diseases, were prepared. Thus, heating N-(4-chlorophenyl)-2-chloro-3-pyridinecarboxamide with 6-aminoindazole at 150° for 2 h afforded II which inhibited VEGF-stimulated HUVEC proliferation at level below 50 nM. Compds. I showed inhibition of KDR at doses less than 50 μM.

IT 454481-33-5P

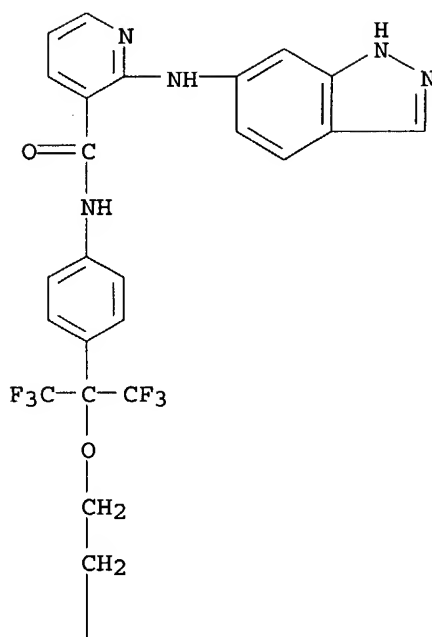
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of substituted 2-(1H-indazol-6-ylamino)nicotinamides for treating KDR-related diseases)

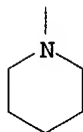
RN 454481-33-5 HCAPLUS

CN 3-Pyridinecarboxamide, 2-(1H-indazol-6-ylamino)-N-[4-[2,2,2-trifluoro-1-[2-(1-piperidinyl)ethoxy]-1-(trifluoromethyl)ethyl]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



L7 ANSWER 3 OF 3 USPATFULL on STN  
 AN 2003:277203 USPATFULL  
 TI Substituted amine derivatives and methods of use  
 IN Chen, Guoqing, Thousand Oaks, CA, UNITED STATES  
 Adams, Jeffrey, Thousand Oaks, CA, UNITED STATES  
 Bemis, Jean, Arlington, MA, UNITED STATES  
 Pietro, Lucian Di, Gloucester, MA, UNITED STATES  
 Dominguez, Celia, Thousand Oaks, CA, UNITED STATES  
 Elbaum, Daniel, Newton, MA, UNITED STATES  
 Germain, Julie, Somerville, MA, UNITED STATES  
 Huang, Qi, Moorpark, CA, UNITED STATES  
 Kim, Joseph L., Wayland, MA, UNITED STATES  
 Ouyang, Xiaohu, Flushing, NY, UNITED STATES  
 Patel, Vinod F., Acton, MA, UNITED STATES  
 Smith, Leon M., Somerset, NJ, UNITED STATES  
 Tasker, Andrew, Simi Valley, CA, UNITED STATES  
 Xi, Ning, Thousand Oaks, CA, UNITED STATES  
 Xu, Shimin, Newbury Park, CA, UNITED STATES  
 Yuan, Chester Chenguang, Newbury Park, CA, UNITED STATES  
 Croghan, Michael, Ventura, CA, UNITED STATES  
 Kim, Tae-Seong, Thousand Oaks, CA, UNITED STATES  
 PI US 2003195230 A1 20031016  
 AI US 2002-46622 A1 20020110 (10)

PRAI US 2001-261882P 20010112 (60)  
US 2001-323808P 20010919 (60)  
DT Utility  
FS APPLICATION  
LREP AMGEN INCORPORATED, MAIL STOP 27-4-A, ONE AMGEN CENTER DRIVE, THOUSAND  
OAKS, CA, 91320-1799  
CLMN Number of Claims: 43  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 9313

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Selected amines are effective for prophylaxis and treatment of diseases, such as angiogenesis mediated diseases. The invention encompasses novel compounds, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compositions and methods for prophylaxis and treatment of diseases and other maladies or conditions involving, cancer and the like. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

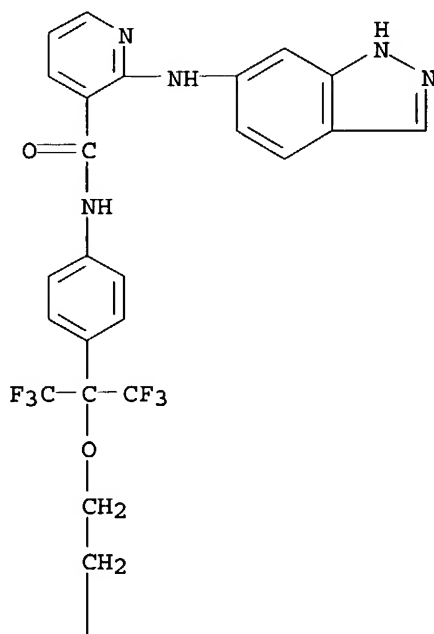
IT 454481-33-5P

(preparation of substituted 2-(1H-indazol-6-ylamino)nicotinamides for treating KDR-related diseases)

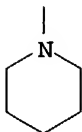
RN 454481-33-5 USPATFULL

CN 3-Pyridinecarboxamide, 2-(1H-indazol-6-ylamino)-N-[4-[2,2,2-trifluoro-1-[2-(1-piperidinyl)ethoxy]-1-(trifluoromethyl)ethyl]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



=> => fil reg

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STRUCTURE FILE UPDATES: 21 JUN 2004 HIGHEST RN 697224-75-2

DICTIONARY FILE UPDATES: 21 JUN 2004 HIGHEST RN 697224-75-2

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

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Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:

<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> d his

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L3 STR L1  
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L5 SCR 1918 OR 2039 OR 2127 OR 2079 OR 2050 OR 2049 OR 2048 OR 205  
L6 3 S L3 AND L4 NOT L5 SAM  
L7 3457123 S (OC5 OR OC4 OR SC4 OR NC4 OR N2C3 OR NCNC2 OR NCOC2 OR NOC3 O  
L8 5 S L3 AND L4 NOT L5 SAM SUB=L7

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L10 11611 S E3-E8  
E E3+ALL  
L11 11979 S E5+OLD,NT,PFT  
E E12+ALL  
L12 2528 S E2+OLD,NT,PFT  
E E12+ALL  
L13 4743 S E4+OLD,NT,PFT  
L14 25222 S ?ANGIOGEN?  
L15 25422 S L10-L14  
L16 16901 S L15 AND (PD<=20010112 OR PRD<=20010112 OR AY<=20010112)

L17 16901 S L16 OR L16  
L18 5000 S L17 RAN=(2001:322960,)  
L19 5000 S L17 RAN=(1999:383117,2001:322939)  
L20 6901 S L17 RAN=(,1999:382518)

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L34 29322 S L33

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L35 2500 S L17 RAN=(2002:156220,)  
L36 2500 S L17 RAN=(2001:322960,2002:155664)

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SET SMARTSELECT ON  
L47       SEL L41 1- RN :   52202 TERMS  
          SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 09:34:46 ON 22 JUN 2004  
L48       52202 S L47

FILE 'HCAPLUS' ENTERED AT 09:38:22 ON 22 JUN 2004  
SET SMARTSELECT ON  
L49       SEL L42 1- RN :   53478 TERMS  
          SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 09:39:05 ON 22 JUN 2004  
L50       53478 S L49

FILE 'HCAPLUS' ENTERED AT 09:42:41 ON 22 JUN 2004  
SET SMARTSELECT ON  
L51       SEL L43 1- RN :   37919 TERMS  
          SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 09:43:24 ON 22 JUN 2004  
L52       37919 S L51

FILE 'HCAPLUS' ENTERED AT 09:45:50 ON 22 JUN 2004  
SET SMARTSELECT ON  
L53       SEL L44 1- RN :   20058 TERMS  
          SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 09:46:21 ON 22 JUN 2004  
L54       20058 S L53

FILE 'HCAPLUS' ENTERED AT 09:47:21 ON 22 JUN 2004  
SET SMARTSELECT ON  
L55       SEL L45 1- RN :   8155 TERMS

SET SMARTSELECT OFF

L56 FILE 'REGISTRY' ENTERED AT 09:47:48 ON 22 JUN 2004  
8155 S L55

FILE 'HCAPLUS' ENTERED AT 09:48:14 ON 22 JUN 2004  
SET SMARTSELECT ON  
L57 SEL L46 1- RN : 36539 TERMS  
SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 09:48:35 ON 22 JUN 2004  
L58 36539 S L57

FILE 'HCAPLUS' ENTERED AT 09:51:20 ON 22 JUN 2004  
L59 400 S L17 RAN=(2002:977961,2003:411091)  
L60 485 S L17 RAN=(2002:574858,2002:977957)  
L61 500 S L17 RAN=(2003:1007109,)  
L62 500 S L41,L42 NOT L59-L61

FILE 'REGISTRY' ENTERED AT 10:39:57 ON 22 JUN 2004

FILE 'HCAPLUS' ENTERED AT 10:39:58 ON 22 JUN 2004  
SET SMARTSELECT ON  
L63 SEL L59 1- RN : 41934 TERMS  
SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 10:40:34 ON 22 JUN 2004  
L64 41934 S L63

FILE 'HCAPLUS' ENTERED AT 10:43:49 ON 22 JUN 2004  
SET SMARTSELECT ON  
L65 SEL L60 1- RN : 35868 TERMS  
SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 10:44:22 ON 22 JUN 2004  
L66 35868 S L65

FILE 'HCAPLUS' ENTERED AT 10:46:44 ON 22 JUN 2004  
SET SMARTSELECT ON  
L67 SEL L61 1- RN : 52202 TERMS  
SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 10:47:12 ON 22 JUN 2004  
L68 52202 S L67

FILE 'HCAPLUS' ENTERED AT 10:50:04 ON 22 JUN 2004  
SET SMARTSELECT ON  
L69 SEL L62 1- RN : 50577 TERMS  
SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 10:50:43 ON 22 JUN 2004  
L70 50577 S L69

FILE 'HCAPLUS' ENTERED AT 10:54:30 ON 22 JUN 2004  
L71 1000 S L61,L62  
L72 1000 S L71 OR L71  
L73 100 S L72 RAN=(2004:371055,)  
L74 100 S L72 RAN=(2004:252604,2004:371053)  
L75 100 S L72 RAN=(2004:142866,2004:252541)  
L76 100 S L72 RAN=(2004:60240,2004:142807)  
L77 100 S L72 RAN=(2003:1007109,2004:60205)  
L78 100 S L72 RAN=(2003:913164,2003:1007021)  
L79 100 S L72 RAN=(2003:818147,2003:913039)

L80 100 S L72 RAN=(2003:719261,2003:818143)  
L81 100 S L72 RAN=(2003:610468,2003:719252)  
L82 100 S L72 RAN=(,2003:610454)

FILE 'REGISTRY' ENTERED AT 11:07:16 ON 22 JUN 2004

FILE 'HCAPLUS' ENTERED AT 11:07:16 ON 22 JUN 2004  
SET SMARTSELECT ON  
L83 SEL L73 1- RN : 30112 TERMS  
SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 11:07:32 ON 22 JUN 2004  
L84 30112 S L83

FILE 'HCAPLUS' ENTERED AT 11:10:12 ON 22 JUN 2004  
SET SMARTSELECT ON  
L85 SEL L74 1- RN : 30109 TERMS  
SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 11:10:27 ON 22 JUN 2004  
L86 30109 S L85

FILE 'HCAPLUS' ENTERED AT 11:12:09 ON 22 JUN 2004  
SET SMARTSELECT ON  
L87 SEL L75 1- RN : 12509 TERMS  
SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 11:12:19 ON 22 JUN 2004  
L88 12509 S L87

FILE 'HCAPLUS' ENTERED AT 11:14:06 ON 22 JUN 2004  
SET SMARTSELECT ON  
L89 SEL L76 1- RN : 11572 TERMS  
SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 11:14:15 ON 22 JUN 2004  
L90 11572 S L89

FILE 'HCAPLUS' ENTERED AT 11:14:57 ON 22 JUN 2004  
SET SMARTSELECT ON  
L91 SEL L78 1- RN : 18549 TERMS  
SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 11:15:09 ON 22 JUN 2004  
L92 18549 S L91

FILE 'HCAPLUS' ENTERED AT 11:16:19 ON 22 JUN 2004  
SET SMARTSELECT ON  
L93 SEL L79 1- RN : 8264 TERMS  
SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 11:16:25 ON 22 JUN 2004  
L94 8264 S L93

FILE 'HCAPLUS' ENTERED AT 11:16:53 ON 22 JUN 2004  
SET SMARTSELECT ON  
L95 SEL L80 1- RN : 9088 TERMS  
SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 11:17:00 ON 22 JUN 2004  
L96 9088 S L95

FILE 'HCAPLUS' ENTERED AT 11:17:30 ON 22 JUN 2004

SET SMARTSELECT ON  
 L97 SEL L81 1- RN : 11056 TERMS  
 SET SMARTSELECT OFF

FILE 'REGISTRY' ENTERED AT 11:17:38 ON 22 JUN 2004

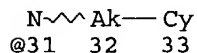
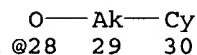
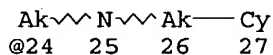
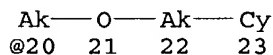
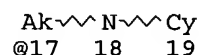
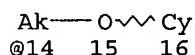
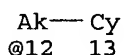
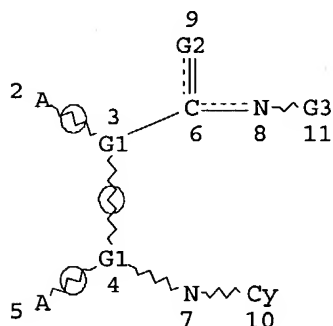
L98 11056 S L97  
 L99 364795 S L24,L26,L28,L32,L34,L38,L40,L48,L50,L52,L54,L56,L58,L64,L66,L  
 L100 4 S L3 SAM SUB=L99  
 L101 212 S L3 FUL SUB=L99  
 SAV L101 KUMAR046/A

FILE 'HCAPLUS' ENTERED AT 11:22:34 ON 22 JUN 2004

L102 68 S L101  
 L103 31 S L102 AND (PD<=20010112 OR PRD<=20010112 OR AD<=20010112)  
 L104 8 S L103 AND L15,L21  
 E AMGEN/PA,CS  
 L105 5 S L103 AND AMGEN?/PA,CS  
 L106 5 S L103 AND (CHEN G? OR ADAMS J? OR BEMIS J? OR DIPIETRO L? OR D  
 L107 2 S L103 AND L9  
 L108 8 S L104-L107  
 L109 61 S L101 (L) (THU OR DMA OR PAC OR PKT)/RL  
 L110 65 S L101 AND (PHARMACEUT? OR PHARMACOL?)/SC,SX  
 L111 30 S L103 AND L109,L110  
 L112 22 S L111 NOT L108

FILE 'REGISTRY' ENTERED AT 11:27:21 ON 22 JUN 2004

=> d 13  
 L3 HAS NO ANSWERS  
 L3 STR



VAR G1=C/N  
 VAR G2=O/S  
 VAR G3=CY/12/14/17/20/24/28/31  
 NODE ATTRIBUTES:  
 DEFAULT MLEVEL IS ATOM  
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
 RING(S) ARE ISOLATED OR EMBEDDED  
 NUMBER OF NODES IS 32

STEREO ATTRIBUTES: NONE

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 11:27:34 ON 22 JUN 2004

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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FILE COVERS 1907 - 22 Jun 2004 VOL 140 ISS 26

FILE LAST UPDATED: 21 Jun 2004 (20040621/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all fhitr tot 1108

L108 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2003:950057 HCAPLUS

DN 140:16647

ED Entered STN: 05 Dec 2003

TI Preparation of 2-aminopyridine-3-carboxamides as remedies for angiogenesis mediated diseases

IN Askew, Benny; Adams, Jeffrey; Booker, Shon; Chen, Guoqing; Dipietro, Lucian V.; Elbaum, Daniel; Germain, Julie; Geuns-Meyer, Stephanie D.; Habgood, Gregory J.; Handley, Michael; Huang, Qi; Kim, Tae-seong; Li, Aiwen; Nishimura, Nobuko; Nomak, Rana; Patel, Vinod F.; Riahi, Babak; Kim, Joseph L.; Xi, Ning; Yang, Kevin; Yuan, Chester Chenguang

PA Amgen Inc., USA

SO U.S. Pat. Appl. Publ., 252 pp., Cont.-in-part of U.S. Ser. No. 46,681. CODEN: USXXCO

DT Patent

LA English

IC ICM A61K031-506

ICS A61K031-4745; A61K031-444; A61K031-4439; C07D471-02; C07D403-02; C07D405-02; C07D413-02

NCL 514256000; 514303000; 514314000; 514332000; 514337000; 514336000; 544333000; 546176000; 546113000; 546262000

CC 27-16 (Heterocyclic Compounds (One Hetero Atom))  
Section cross-reference(s): 1, 63

FAN.CNT 2

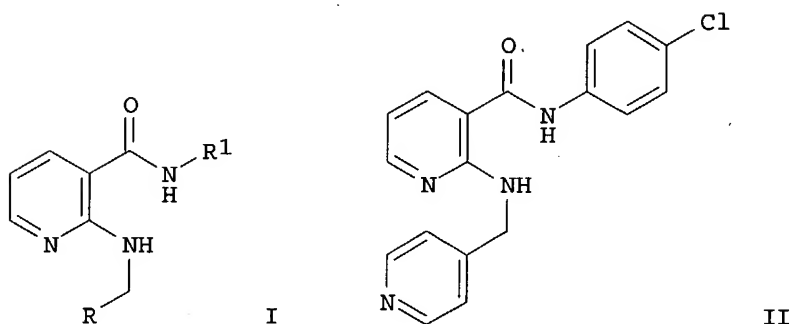
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003225106	A1	20031204	US 2002-197974	20020717 <--
	US 2003125339	A1	20030703	US 2002-46681	20020110 <--
	WO 2004007458	A1	20040122	WO 2003-US22417	20030715
	W:		AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,		

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
 LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,  
 PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,  
 UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,  
 TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,  
 CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,  
 NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,  
 GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-261339P P 20010112 <--  
 US 2001-323764P P 20010919  
 US 2002-46681 A2 20020110  
 US 2002-197974 A 20020717

OS MARPAT 140:16647  
 GI



- AB The title compds. [I; R = (un)substituted 4-pyridyl, 2-pyridyl, 4-pyrimidinyl, 4-quinolyl, etc.; R1 = (un)substituted aryl, cycloalkyl, 5-6 membered heteroaryl, 9-10 membered bicyclic and 11-14 membered tricyclic heterocyclyl], which are effective for prophylaxis and treatment of diseases and other maladies or conditions involving, cancer and the like, were prepared Thus, the title compound II was prepared from 2-aminonicotinic acid, 4-chloroaniline, and 4-pyridinecarboxaldehyde. The compds. I showed inhibition of KDR kinase at < 50  $\mu$ M. Many compds. I inhibited VEGF-stimulated HUVEC proliferation at a level below 50 nM. Pharmaceutical composition comprising the compound I is claimed.
- ST aminopyridinecarboxamide prepn antitumor VEGFR KDR kinase inhibitor; pyridinecarboxamide prepn **angiogenesis** mediated disease VEGFR KDR kinase inhibitor
- IT Cytotoxic agents  
 (antimetabolites, co-administration; preparation of 2-aminopyridine-3-carboxamides for treating **angiogenesis** mediated diseases)
- IT Interferons  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (co-administration with interferon-type agents; preparation of 2-aminopyridine-3-carboxamides for treating **angiogenesis** mediated diseases)
- IT Alkylating agents, biological  
 Antibiotics  
 Immunomodulators  
 (co-administration; preparation of 2-aminopyridine-3-carboxamides for treating **angiogenesis** mediated diseases)
- IT Hormones, animal, biological studies  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (co-administration; preparation of 2-aminopyridine-3-carboxamides for

- treating **angiogenesis** mediated diseases)
- IT Eye, disease  
(diabetic retinopathy, treatment of; preparation of 2-aminopyridine-3-carboxamides for treating **angiogenesis** mediated diseases)
- IT **Angiogenesis**  
(neovascularization, eye, treatment of corneal neovascularization; preparation of 2-aminopyridine-3-carboxamides for treating **angiogenesis** mediated diseases)
- IT Eye, disease  
(neovascularization, treatment of corneal neovascularization; preparation of 2-aminopyridine-3-carboxamides for treating **angiogenesis** mediated diseases)
- IT **Angiogenesis**  
**Angiogenesis inhibitors**  
 Anti-inflammatory agents  
 Antitumor agents  
 Cell proliferation  
 Human  
 Inflammation  
 Neoplasm  
 (preparation of 2-aminopyridine-3-carboxamides for treating **angiogenesis** mediated diseases)
- IT 150977-45-0  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (preparation of 2-aminopyridine-3-carboxamides for treating **angiogenesis** mediated diseases)
- IT 453561-03-0P 453561-73-4P 453561-77-8P 453561-95-0P 453562-69-1P  
 453562-83-9P 453563-07-0P 453563-37-6P 453563-79-6P 453564-01-7P  
 629651-31-6P 629651-56-5P  
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (preparation of 2-aminopyridine-3-carboxamides for treating **angiogenesis** mediated diseases)
- IT 352227-57-7P, 2-[(Pyridin-4-ylmethyl)amino]-N-(3-trifluoromethylphenyl)nicotinamide 352227-65-7P 352227-72-6P  
 352227-74-8P 453560-98-0P 453561-00-7P 453561-01-8P 453561-02-9P  
 453561-04-1P 453561-05-2P 453561-06-3P 453561-07-4P 453561-08-5P  
 453561-09-6P 453561-11-0P 453561-12-1P 453561-13-2P 453561-14-3P  
 453561-15-4P 453561-16-5P 453561-17-6P 453561-18-7P 453561-20-1P  
 453561-21-2P 453561-22-3P 453561-23-4P 453561-24-5P 453561-26-7P  
 453561-27-8P 453561-29-0P 453561-32-5P 453561-33-6P 453561-34-7P  
 453561-35-8P 453561-36-9P 453561-37-0P 453561-38-1P 453561-39-2P  
 453561-40-5P 453561-41-6P 453561-42-7P 453561-43-8P 453561-44-9P  
 453561-45-0P 453561-46-1P 453561-47-2P 453561-48-3P 453561-49-4P  
 453561-50-7P 453561-51-8P 453561-53-0P 453561-54-1P 453561-55-2P  
 453561-56-3P 453561-57-4P 453561-58-5P 453561-59-6P 453561-60-9P  
 453561-61-0P 453561-62-1P 453561-63-2P 453561-64-3P 453561-65-4P  
 453561-67-6P 453561-68-7P 453561-69-8P 453561-70-1P 453561-71-2P  
 453561-72-3P 453561-75-6P 453561-76-7P 453561-78-9P 453561-80-3P  
 453561-81-4P, 2-[(2,3-Dihydrobenzofuran-5-ylmethyl)amino]-N-[3,3-dimethyl-1-(piperidin-4-ylmethyl)-2,3-dihydro-1H-indol-6-yl]nicotinamide  
 453561-82-5P 453561-83-6P 453561-84-7P 453561-85-8P,  
 N-[1-(2-Aminoacetyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl]-2-[(2-methoxy-pyridin-4-ylmethyl)amino]nicotinamide 453561-86-9P,  
 N-[1-(2-Aminoacetyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl]-2-[(pyridin-4-ylmethyl)amino]nicotinamide 453561-87-0P, (S)-N-[3-(Pyrrolidin-2-ylmethoxy)-4-pentafluoroethylphenyl]-2-[(pyridin-4-ylmethyl)amino]nicotinamide 453561-88-1P, (R)-N-[3-(Pyrrolidin-2-ylmethoxy)-4-trifluoromethylphenyl]-2-[(pyridin-4-ylmethyl)amino]nicotinamide 453561-89-2P, (R)-N-[3-(Pyrrolidin-2-ylmethoxy)-4-pentafluoroethylphenyl]-2-[(pyridin-4-ylmethyl)amino]nicotinamide 453561-90-5P, (S)-N-[3-(Pyrrolidin-2-

ylmethoxy)-5-trifluoromethylphenyl]-2-[(pyridin-4-ylmethyl)amino]nicotinamide 453561-92-7P, N-[3-(Piperidin-4-yloxy)-5-trifluoromethylphenyl]-2-[(pyridin-4-ylmethyl)amino]nicotinamide 453561-93-8P, N-[4-tert-Butyl-3-[(piperidin-4-yl)methoxy]phenyl]-2-[(pyridin-4-ylmethyl)amino]nicotinamide 453561-94-9P, N-[4-tert-Butyl-3-(pyrrolidin-2-ylmethoxy)phenyl]-2-[(pyridin-4-ylmethyl)amino]nicotinamide 453561-96-1P 453561-97-2P 453561-98-3P 453561-99-4P 453562-00-0P 453562-02-2P 453562-03-3P 453562-05-5P 453562-07-7P 453562-08-8P 453562-09-9P 453562-10-2P 453562-11-3P 453562-12-4P 453562-13-5P 453562-14-6P 453562-15-7P 453562-16-8P 453562-18-0P 453562-19-1P 453562-20-4P 453562-21-5P 453562-22-6P 453562-23-7P 453562-24-8P 453562-25-9P 453562-26-0P 453562-27-1P 453562-28-2P 453562-29-3P 453562-30-6P 453562-31-7P 453562-32-8P 453562-34-0P 453562-35-1P 453562-36-2P 453562-37-3P 453562-38-4P 453562-39-5P 453562-40-8P 453562-41-9P 453562-42-0P 453562-43-1P 453562-44-2P 453562-45-3P 453562-47-5P 453562-48-6P 453562-49-7P 453562-52-2P 453562-55-5P 453562-56-6P 453562-57-7P 453562-61-3P 453562-62-4P 453562-65-7P 453562-66-8P 453562-75-9P 453562-76-0P 453562-80-6P 453562-81-7P 453562-84-0P 453562-85-1P 453562-86-2P 453562-87-3P 453562-91-9P 453562-92-0P 453562-93-1P 453562-94-2P 453562-96-4P 453562-98-6P 453562-99-7P 453563-00-3P 453563-02-5P 453563-06-9P 453563-08-1P 453563-10-5P 453563-11-6P 453563-12-7P 453563-13-8P 453563-14-9P 453563-15-0P 453563-16-1P 453563-17-2P 453563-18-3P 453563-20-7P 453563-21-8P 453563-22-9P 453563-23-0P 453563-24-1P 453563-25-2P 453563-26-3P 453563-27-4P 453563-28-5P 453563-29-6P 453563-32-1P 453563-33-2P 453563-34-3P 453563-35-4P 453563-36-5P 453563-38-7P 453563-39-8P 453563-40-1P 453563-41-2P 453563-42-3P 453563-43-4P 453563-44-5P 453563-45-6P 453563-46-7P 453563-47-8P 453563-48-9P 453563-49-0P 453563-50-3P 453563-51-4P 453563-52-5P 453563-53-6P 453563-54-7P 453563-55-8P 453563-56-9P 453563-57-0P 453563-58-1P 453563-59-2P 453563-60-5P 453563-61-6P 453563-62-7P 453563-63-8P 453563-64-9P 453563-65-0P 453563-66-1P 453563-67-2P 453563-68-3P 453563-69-4P 453563-70-7P 453563-71-8P 453563-72-9P 453563-73-0P 453563-74-1P 453563-75-2P 453563-76-3P 453563-77-4P 453563-78-5P 453563-80-9P 453563-81-0P 453563-82-1P 453563-83-2P 453563-84-3P 453563-85-4P 453563-86-5P 453563-87-6P 453563-88-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-aminopyridine-3-carboxamides for treating angiogenesis mediated diseases)

IT	453563-89-8P	453563-90-1P	453563-91-2P	453563-92-3P	453563-93-4P
	453563-94-5P	453563-95-6P	453563-96-7P	453563-97-8P	453563-98-9P
	453563-99-0P	453564-00-6P	453564-02-8P	453564-03-9P	453564-04-0P
	453564-05-1P	453564-06-2P	453564-07-3P	453564-08-4P	453564-09-5P
	453564-10-8P	453564-11-9P	453564-12-0P	453564-13-1P	453564-14-2P
	453564-15-3P	<b>453564-16-4P</b>	453564-17-5P	453564-18-6P	
	453564-19-7P	453564-20-0P	453564-21-1P	453564-22-2P	453564-23-3P
	453564-24-4P	453564-25-5P	453564-26-6P	453564-27-7P	453564-28-8P
	453564-30-2P	453564-31-3P	453564-32-4P	453564-33-5P	453564-34-6P
	453564-36-8P	453564-37-9P	453564-38-0P	453564-39-1P	453564-40-4P
	453564-41-5P	453564-42-6P	453564-43-7P	453564-44-8P	453564-45-9P
	453564-80-2P	453565-02-1P	453565-03-2P	453565-04-3P	453565-05-4P
	453565-06-5P	453565-07-6P	453565-08-7P	453565-09-8P	453565-10-1P
	453565-11-2P	453565-12-3P	453565-13-4P	453565-14-5P	453565-15-6P
	453565-16-7P	453565-17-8P	453565-18-9P	453565-19-0P	453565-20-3P
	453565-21-4P	453565-22-5P	453565-23-6P	453565-24-7P	453565-25-8P
	453565-26-9P	453565-27-0P	453565-28-1P	453565-29-2P	453565-30-5P
	453565-31-6P	453565-32-7P	453565-33-8P	629650-29-9P	629650-30-2P
	629650-31-3P	629650-32-4P	629650-33-5P	629650-34-6P	629650-35-7P
	629650-36-8P	629650-37-9P	629650-38-0P	629650-39-1P	629650-40-4P
	629650-41-5P	629650-42-6P	629650-43-7P	629650-44-8P	629650-45-9P

629650-46-0P	629650-47-1P	629650-48-2P	629650-49-3P	629650-50-6P
629650-51-7P	629650-52-8P	629650-53-9P	629650-54-0P	629650-55-1P
629650-56-2P	629650-57-3P	629650-58-4P	629650-59-5P	629650-60-8P
629650-61-9P	629650-62-0P	629650-63-1P	629650-64-2P	629650-65-3P
629650-66-4P	629650-67-5P	629650-68-6P	629650-69-7P	629650-70-0P
629650-71-1P	629650-72-2P	629650-73-3P	629650-74-4P	629650-75-5P
629650-76-6P	629650-77-7P	629650-78-8P	629650-79-9P	629650-80-2P
629650-81-3P	629650-82-4P	629650-83-5P	629650-84-6P	629650-85-7P
629650-86-8P	629650-87-9P	629650-88-0P	629650-89-1P	629650-90-4P
629650-91-5P	629650-92-6P	629650-93-7P	629650-94-8P	629650-95-9P
629650-96-0P	629650-97-1P	629650-98-2P	629650-99-3P	629651-00-9P
629651-01-0P	629651-02-1P	629651-03-2P	629651-04-3P	629651-05-4P
629651-06-5P	629651-07-6P	629651-08-7P	629651-09-8P	629651-10-1P
629651-11-2P	629651-12-3P	629651-13-4P	629651-14-5P	629651-15-6P
629651-16-7P	629651-17-8P	629651-18-9P	629651-19-0P	629651-20-3P
629651-21-4P	629651-22-5P	629651-23-6P	629651-24-7P	629651-25-8P
629651-26-9P	629651-27-0P	629651-28-1P	629651-29-2P	629651-30-5P
629651-32-7P	629651-33-8P	629651-34-9P	629651-35-0P	629651-36-1P
629651-37-2P	629651-38-3P	629651-39-4P	<b>629651-40-7P</b>	
629651-41-8P	629651-42-9P	629651-43-0P	629651-44-1P	629651-45-2P
629651-46-3P	629651-47-4P	629651-48-5P	629651-49-6P	629651-50-9P
629651-51-0P	629651-53-2P	629651-54-3P	629651-55-4P	629651-57-6P
629651-58-7P	629651-59-8P	629651-60-1P	629651-61-2P	629651-62-3P
629651-63-4P	629651-64-5P	629651-65-6P	629651-66-7P	629651-67-8P
629651-68-9P	629651-69-0P	629651-70-3P	629651-71-4P	629651-72-5P
629651-73-6P	629651-74-7P	629651-75-8P	629651-76-9P	629651-77-0P
629651-78-1P	629651-79-2P			

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-aminopyridine-3-carboxamides for treating **angiogenesis** mediated diseases)

IT	629651-80-5P	629651-81-6P	629651-82-7P	629651-83-8P	629651-84-9P
	629651-85-0P	629651-86-1P	629651-87-2P	629651-88-3P	629651-89-4P
	629651-90-7P	629651-91-8P	629651-92-9P	629651-93-0P	629651-94-1P
	629651-98-5P	629651-99-6P	629652-00-2P	629652-01-3P	629652-02-4P
	629652-03-5P	629656-02-6P			

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-aminopyridine-3-carboxamides for treating **angiogenesis** mediated diseases)

IT	55-86-7	79-04-9, Chloroacetyl chloride	98-16-8, 3-(Trifluoromethyl)aniline	99-09-2, 3-Nitroaniline	99-57-0, 2-Amino-4-nitrophenol	99-88-7, 4-Isopropylaniline	106-47-8, 4-Chloroaniline, reactions	106-52-5, 4-Hydroxy-1-methylpiperidine	108-01-0, N,N-Dimethylethanolamine	108-23-6, Isopropyl chloroformate	109-01-3, N-Methylpiperazine	109-72-8, Butyllithium, reactions	110-89-4, Piperidine, reactions	121-51-7, 3-Nitrobenzenesulfonyl chloride	123-00-2, 4-Morpholinepropanamine	139-59-3, 4-Phenoxyaniline	288-88-0, 1H-1,2,4-Triazole	328-79-0, 1-Methoxy-3-nitro-5-trifluoromethylbenzene	328-80-3	350-46-9, 1-Fluoro-4-nitrobenzene	372-48-5, 2-Fluoropyridine	527-72-0, 2-Thienylcarboxylic acid	541-41-3, Ethyl chloroformate	609-71-2, 2-Hydroxynicotinic acid	628-13-7, Pyridine hydrochloride	722-92-9, 2-(4-Aminophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol	769-92-6, 4-tert-Butylaniline	872-85-5, 4-Pyridinecarboxaldehyde	1083-48-3, 4-(4-Nitrobenzyl)pyridine	1118-68-9, Dimethylaminoacetic acid	1126-09-6, Piperidine-4-carboxylic acid ethyl ester	1445-73-4, N-Methyl-4-piperidone	1458-98-6, 3-Bromo-2-methylpropene	1692-15-5, 4-Pyridylboronic acid	1704-62-7, 2-[2-(Dimethylamino)ethoxy]ethanol	2008-75-5, 1-(2-Chloroethyl)piperidine hydrochloride	2221-00-3, (4-Imidazolylphenyl)amine	2435-50-9, Pyrimidine-4-carboxaldehyde
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2942-59-8, 2-Chloronicotinic acid 3040-44-6, 2-(Piperid-1-yl)ethanol  
 3279-07-0, 2-Nitro-4-tert-butylphenol 3282-56-2, 4-tert-  
 Butylnitrobenzene 3438-46-8, 4-Methylpyrimidine 3554-65-2 3647-69-6,  
 4-(2-Chloroethyl)morpholine hydrochloride 3731-53-1,  
 4-Aminomethylpyridine 4009-98-7, Methoxymethyltriphenylphosphonium  
 chloride 4160-54-7, 1,3-Dinitro-4-tert-butylbenzene 4769-96-4,  
 6-Nitroindole 5345-47-1, 2-Aminonicotinic acid 5458-84-4,  
 2-Iodo-5-nitroanisole 5909-24-0, Ethyl 4-chloro-2-methylthiopyrimidine-5-  
 carboxylate 6146-52-7, 5-Nitroindole 6165-69-1, 3-Thiopheneboronic  
 acid 6310-21-0, 2-tert-Butylaniline 6457-49-4, 4-Piperidylmethanol  
 7216-42-4 7223-38-3, 1-Dimethylamino-2-propyne 10403-47-1,  
 2-Bromo-5-nitroaniline 13258-63-4, 4-(2-Aminoethyl)pyridine  
 14446-67-4, 1-Allylpiperidine 19727-83-4, 6-Nitroindoline 19910-33-9,  
 2-(4-Nitrophenyl)propionic acid 20769-85-1, 2-Bromo-2-methylpropionyl  
 bromide 22288-78-4, Methyl 3-amino-2-thiophenecarboxylate 24424-99-5,  
 Di-tert-butyl dicarbonate 24954-67-4, 2-(4-Nitrophenyl)ethylamine  
 30529-70-5, 2-Chloro-6-methylnicotinic acid 33252-30-1,  
 2-Chloro-4-cyanopyridine 51149-08-7 54962-75-3, 3-Bromo-5-  
 (trifluoromethyl)phenylamine 57260-71-6, N-Boc-piperazine 60979-14-8,  
 1-Nitro-4-(1,1,2,2,2-pentafluoroethyl)benzene 69610-40-8 71999-74-1  
 74764-17-3, 2-(2-Pyridylamino)ethylamine 75833-38-4,  
 2-Chloropyrimidine-4-carbonitrile 80887-01-0, 2-Bromo-5-nitrobenzoyl  
 chloride 102362-98-1, 3,3-Dimethyl-2,3-dihydrobenzo[d]isothiazole  
 1,1-dioxide 105612-50-8 109384-19-2, 1-Boc-4-hydroxypiperidine  
 110073-17-1, Methyl 2-(morpholin-4-yl)propionate 119899-26-2,  
 2-Fluoropyridine-3-carbonyl chloride 148546-99-0, 3-(4-  
 Methylpiperazinyl)phenylamine 171178-50-0, 2,6-Difluoropyridine-3-  
 carboxylic acid 183946-06-7, 2-Methyl-4-nitro-1-pentafluoroethylbenzene  
 201733-56-4 453560-55-9, 1-Boc-2-(3-nitro-5-  
 trifluoromethylphenoxy)methylpyrrolidine 453560-61-7,  
 3,3-Dimethyl-1-(1-Boc-piperidin-4-ylmethyl)-6-nitro-2,3-dihydro-1H-indole  
 453560-62-8 453560-64-0, 2-Methoxy-4-nitro-1-pentafluoroethylbenzene  
 453560-68-4 453560-72-0, (S)-2-Chloro-N-[4-(2-oxiranylmethoxy)-3-  
 pentafluoroethylphenyl]nicotinamide 453560-93-5, 1-Methyl-4-[1-methyl-1-  
 (4-nitrophenyl)ethyl]pyridinium 453561-19-8 453561-74-5 453563-30-9,  
 2-Fluoro-N-(4-trifluoromethylphenyl)nicotinamide 453563-31-0,  
 [[2-(1-Isopropylazetidin-3-ylmethoxy)pyridin-4-yl]methyl]amine  
 453564-35-7, 2-Amino-N-(4-pentafluoroethylphenyl)nicotinamide  
 618446-18-7 618446-37-0 618446-39-2

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of 2-aminopyridine-3-carboxamides for treating  
 angiogenesis mediated diseases)

IT 349-57-5P, 3-Nitro-5-trifluoromethylphenol 393-55-5P, 2-Fluoronicotinic  
 acid 6310-17-4P, 2-Bromo-1-tert-butyl-4-nitrobenzene 6425-46-3P,  
 4-[(4-Nitrophenyl)methyl]morpholine 13669-28-8P, 1-Methyl-4-  
 methylenepiperidine 16153-81-4P, 4-Methyl-1-(4-aminophenyl)piperazine  
 16155-03-6P, 4-Methyl-1-(4-nitrophenyl)piperazine 18755-53-8P,  
 2-Methyl-2-(4-nitrophenyl)propan-1-ol 20691-89-8P, (1-Methylpiperidin-4-  
 yl)methanol 24252-37-7P, 1-Methylpiperidine-4-carboxylic acid ethyl  
 ester 29241-65-4P, 5-Bromo-2-chloronicotinic acid 51013-67-3P,  
 4-(Morpholin-4-ylmethyl)phenylamine 51444-31-6P, 2-(1,2,4-  
 Triazolyl)ethylamine 53062-99-0P 54815-23-5P, 2-(4-Aminophenyl)-2-  
 methylpropionic acid methyl ester 56329-05-6P 57841-51-7P  
 59115-08-1P, 2-Methyl-2-(4-nitrophenyl)propionic acid methyl ester  
 60979-04-6P, 4-(1,1,2,2,2-Pentafluoroethyl)phenylamine 69296-06-6P,  
 2-Morpholin-4-ylpropanol 72716-86-0P, 4-Cyano-2-methoxypyridine  
 85160-84-5P, 2,2-Dimethyl-6-nitro-4H-benzo[1,4]oxazin-3-one 90221-50-4P,  
 N-(2-Bromo-5-nitrophenyl)acetamide 91133-58-3P 94838-59-2P  
 100973-67-9P 101537-64-8P, 3-[(tert-Butoxy)carbonylamino]thiophene-2-  
 carboxylic acid 103392-84-3P, 2-tert-Butyl-5-nitroaniline  
 103394-70-3P, 4-tert-Butyl-3-nitrophenylamine 104612-36-4P,  
 5-Bromo-2-hydroxynicotinic acid 105807-77-0P, 2,2,4-Trimethyl-6-nitro-4H-  
 benzo[1,4]oxazin-3-one 105807-84-9P, 6-Amino-2,2-dimethyl-4H-

benzo[1,4]oxazin-3-one 106516-27-2P, 3-(1-Methyl-1,2,3,6-tetrahydropyridin-4-yl)-5-nitro-1H-indole 117242-06-5P, 4,4-Dimethyl-7-nitro-3,4-dihydro-2H-isoquinolin-1-one 136545-11-4P, 2,2-Dimethyl-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine 137076-22-3P, 1-Boc-4-formylpiperidine 140837-70-3P, 3,3-Dimethyl-6-nitro-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide 142253-56-3P, 1-Boc-3-Hydroxymethylazetidine 142253-57-4P, Methanesulfonic acid N-Boc-azetidin-3-ylmethyl ester 142851-03-4P, 1-Boc-piperidine-4-carboxylic acid ethyl ester 143094-45-5P, 5-Bromo-2-chloro-N-(4-chlorophenyl)nicotinamide 144226-16-4P 144293-82-3P, 1-(2,2-Dimethyl-6-nitro-2,3-dihydrobenzo[1,4]oxazin-4-yl)ethanone 144293-83-4P, 1-(6-Amino-2,2-dimethyl-2,3-dihydrobenzo[1,4]oxazin-4-yl)ethanone 148900-69-0P, ((2-Methoxy-4-pyridyl)methyl)amine 149532-90-1P, ((2-Methoxypyridin-4-yl)methyl)amine hydrochloride 161975-39-9P, 1-Boc-4-methylsulfonyloxymethylpiperidine 179898-72-7P, 3,3-Dimethyl-6-nitroindoline 180692-27-7P, Trifluoromethanesulfonic acid 1-methyl-1,2,3,6-tetrahydropyridin-4-yl ester 181363-19-9P 182564-38-1P, 3-(1-Methyl-4-piperidyl)indole-5-ylamine 436095-35-1P, 3-[(4-Methylpiperazinyl)sulfonyl]phenylamine 442846-54-0P, [(2-(1-Methylpiperidin-4-yloxy)pyridin-4-yl)methyl]amine 442846-55-1P, [(2-(1-Methylpyrrolidin-2-ylmethoxy)pyridin-4-yl)methyl]amine 442846-56-2P, (4-Aminomethylpyridin-2-yl)(3-morpholin-4-ylpropyl)amine 442846-58-4P, [(2-(1-Methylpiperidin-4-ylmethoxy)pyridin-4-yl)methyl]amine 442846-59-5P, 3-(4-Boc-piperazin-1-ylmethyl)-5-trifluoromethylphenylamine 442846-60-8P, (3-(4-Methylpiperazin-1-ylmethyl)-4-pentafluoroethylphenyl)amine 442846-61-9P, 7-Amino-2-(4-methoxybenzyl)-4,4-dimethyl-3,4-dihydro-2H-isoquinolin-1-one 442846-62-0P, (3-Amino-5-trifluoromethylphenyl)(4-Boc-piperazin-1-yl)methanone 442846-63-1P, 1-(7-Amino-4,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)ethanone 442846-64-2P, 4-tert-Butyl-3-(1-Boc-pyrrolidin-3-ylmethoxy)phenylamine 442846-65-3P, 4-tert-Butyl-3-(1-Boc-azetidin-3-ylmethoxy)phenylamine 442846-67-5P, N-(4-Acetyl-2,2-dimethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-fluoronicotinamide 442846-68-6P, 2-Fluoro-N-(2,2,4-trimethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)nicotinamide 442846-69-7P, N-(2,2-Dimethyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-fluoronicotinamide 442846-70-0P, 2-Fluoro-N-[3-(4-methylpiperazin-1-ylmethyl)-5-trifluoromethylphenyl]nicotinamide 442846-71-1P, 2-Fluoro-N-(2-Boc-4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)nicotinamide 442846-72-2P, 2-Fluoro-N-[3-(4-methylpiperazin-1-ylmethyl)-4-pentafluoroethylphenyl]nicotinamide 442846-73-3P, 2-Fluoro-N-(4,4-dimethyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)nicotinamide 442846-74-4P, 2-Fluoro-N-[3-((4-Boc-piperazin-1-yl)carbonyl)-5-trifluoromethylphenyl]nicotinamide 442846-75-5P, 2-Fluoro-N-[3-(4-Boc-piperazin-1-ylmethyl)-5-trifluoromethylphenyl]nicotinamide 442846-76-6P, N-(2-Acetyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-fluoronicotinamide 442846-77-7P, N-[3,3-Dimethyl-1-(1-methylpiperidin-4-yl)-2,3-dihydro-1H-indol-6-yl]-2-fluoronicotinamide 442846-78-8P, 2-Fluoro-N-[3-(1-Boc-azetidin-3-ylmethoxy)-5-trifluoromethylphenyl]nicotinamide 442846-79-9P, (S)-N-[4-tert-Butyl-3-(1-Boc-pyrrolidin-2-ylmethoxy)phenyl]-2-fluoronicotinamide 442846-80-2P, 2-Chloro-N-[2-(4-methoxybenzyl)-4,4-dimethyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]nicotinamide 442846-81-3P, 2-Chloro-N-(4,4-dimethyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)nicotinamide 442846-82-4P, 2-[3-[(2-Chloropyridine-3-carbonyl)aminophenyl]-2-methylpropionic acid methyl ester 442846-83-5P, N-[4-tert-Butyl-3-[2-(1-Boc-piperidin-4-yl)ethyl]phenyl]-2-chloronicotinamide 442846-84-6P 442846-85-7P 442846-86-8P 442846-87-9P 442846-88-0P, 1-[2-(2-tert-Butyl-5-nitrophenoxy)ethyl]piperidine 442846-90-4P 442846-91-5P, 1-(4,4-Dimethyl-7-nitro-3,4-dihydro-1H-isoquinolin-2-yl)ethanone 442846-92-6P, 2-Bromo-N-(4-methoxybenzyl)-5-nitrobenzamide 442846-93-7P, 4,4-Dimethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline 442846-94-8P,

1-Boc-4-(3-nitro-5-trifluoromethylbenzyl)piperazine 442846-97-1P,  
1-Methyl-4-[1-methyl-1-(4-nitrophenyl)ethyl]pyridinium iodide  
442846-98-2P, 1-Methyl-4-(4-nitrobenzyl)-1,2,3,6-tetrahydropyridine  
442847-02-1P 442847-03-2P, [3-[3-Amino-5-(trifluoromethyl)phenyl]propyn-  
2-yl]dimethylamine 442847-04-3P, [3-[3-Amino-5-  
(trifluoromethyl)phenyl]propyl]dimethylamine 442847-06-5P,  
4-(2-tert-Butyl-5-nitrophenyl)pyridine 442847-07-6P 442847-08-7P,  
4-tert-Butyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)aniline  
442847-11-2P, 2-tert-Butyl-5-nitrophenol 452929-03-2P,  
1-(2-tert-Butylphenyl)-4-methylpiperazine 453560-49-1P,  
1-Boc-4-(3-nitro-5-trifluoromethylphenoxy)piperidine 453560-50-4P,  
1-Boc-4-(3-amino-5-trifluoromethylphenoxy)piperidine 453560-51-5P,  
(S)-4-tert-Butyl-3-(1-Boc-pyrrolidin-2-ylmethoxy)phenylamine  
453560-52-6P 453560-53-7P, N-[3-(1-Methylpiperidin-4-yl)-5-  
trifluoromethylphenyl]-2-fluoronicotinamide 453560-54-8P,  
2-(3-Nitro-5-trifluoromethylphenoxyethyl)pyrrolidine 453560-56-0P,  
1-Methyl-2-(3-nitro-5-trifluoromethylphenoxyethyl)pyrrolidine  
453560-57-1P, N-(3-Bromo-5-trifluoromethylphenyl)acetamide 453560-58-2P  
453560-59-3P 453560-60-6P, 3,3-Dimethyl-6-nitro-1-(piperidin-4-ylmethyl)-  
2,3-dihydro-1H-indole 453560-63-9P, 5-Nitro-2-pentafluoroethylphenol  
453560-66-2P 453560-67-3P 453560-69-5P 453560-70-8P 453560-71-9P,  
(S)-2-Chloro-N-[4-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-3-  
pentafluoroethylphenyl]nicotinamide 453560-73-1P 453560-74-2P,  
5-Nitro-2-trifluoromethylanisole 453560-76-4P 453560-77-5P,  
(R)-2-Chloro-N-[3-(2-hydroxy-2-(pyrrolidin-1-yl)propoxy)-4-  
pentafluoroethylphenyl]nicotinamide 453560-78-6P, 2-Dimethylamino-1-(3,3-  
dimethyl-6-nitro-2,3-dihydroindol-1-yl)ethanone 453560-79-7P  
453560-80-0P, 2-Boc-4,4-dimethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline  
453560-81-1P 453560-82-2P, 2-(4-Methoxybenzyl)-4,4-dimethyl-7-nitro-3,4-  
dihydro-2H-isoquinolin-1-one 453560-83-3P, 2-Bromomethyl-4-nitro-1-  
pentafluoroethylbenzene 453560-84-4P 453560-85-5P 453560-86-6P,  
(4-Boc-piperazin-1-yl)(3-nitro-5-trifluoromethylphenyl)methanone  
453560-87-7P 453560-88-8P 453560-89-9P, 3-(5,5-Dimethyl-  
[1,3,2]dioxaborinan-2-yl)-5-trifluoromethylphenylamine 453560-90-2P,  
1-Boc-3-(3-nitro-5-trifluoromethylphenoxyethyl)azetidine 453560-91-3P,  
2-Bromo-N-(2-hydroxy-5-nitrophenyl)-2-methylpropionamide 453560-92-4P,  
4-[1-(2-Bromo-4-nitrophenyl)-1-methylethyl]-1-methylpyridinium iodide  
453560-94-6P, 4-[1-(2-Bromo-4-nitrophenyl)-1-methylethyl]-1-methyl-1,2,3,6-  
tetrahydropyridine 453560-95-7P, 4-(2-tert-Butyl-5-nitrophenyl)but-3-en-  
1-ol 453560-96-8P, 4-(2-tert-Butyl-5-nitrophenyl)but-3-enal  
453560-97-9P, 1-[4-(2-tert-Butyl-5-nitrophenyl)but-3-enyl]pyrrolidine  
453560-99-1P 453561-10-9P, 6-Methyl-2-[(4-pyridylmethyl)amino]pyridine-3-  
carboxylic acid 453561-25-6P, 5-(3-Thiophene)-2-chloro-N-(4-  
chlorophenyl)nicotinamide 453561-30-3P 453561-31-4P 453562-01-1P,  
3-[(4-Methylpiperazinyl)sulfonyl]-1-nitrobenzene 453562-06-6P  
453562-50-0P, [2-[4-(tert-Butyl)-2-nitrophenoxy]ethyl]dimethylamine  
453562-51-1P, [2-[4-(tert-Butyl)-2-aminophenoxy]ethyl]dimethylamine  
453562-53-3P, 1-[2-(tert-Butyl)-5-aminophenyl]-4-methylpiperazine  
453562-54-4P, 1-[2-(tert-Butyl)-5-nitrophenyl]-4-methylpiperazine  
453562-59-9P 453562-60-2P, 1-(1-Methyl-4-piperidyl)indoline-6-ylamine  
453562-63-5P, 1-(6-Nitroindolinyl)-2-piperidylethan-1-one 453562-64-6P,  
1-(2-Piperidylethyl)indoline-6-ylamine 453562-67-9P,  
N-(2-Bromo-5-nitrophenyl)-N-(2-methylprop-2-enyl)acetamide 453562-68-0P  
453562-71-5P, 1-Acetyl-6-amino-3,3-dimethylindoline 453562-74-8P  
453562-77-1P, 2-Methyl-2-(4-nitrophenyl)propionaldehyde 453562-78-2P,  
4-[3-Methyl-3-(4-nitrophenyl)butyl]morpholine 453562-79-3P,  
4-(1,1-Dimethyl-3-(morpholin-4-yl)propyl)phenylamine 453562-88-4P,  
(2E)-3-[2-(tert-Butyl)-5-nitrophenyl]-1-(piperid-1-yl)prop-2-en-1-one  
453562-89-5P, (2E)-3-[2-(tert-Butyl)-5-aminophenyl]-1-(piperid-1-yl)prop-2-  
en-1-one 453562-90-8P, 4-(tert-Butyl)-3-(3-piperidylpropyl)phenylamine  
453562-95-3P, (1-(2-(Morpholin-4-yl)ethyl)indole-6-yl)amine 453563-01-4P  
453563-03-6P, 2-[2-[2-(Dimethylamino)ethoxy]ethoxy]pyridine-4-carbonitrile  
453563-04-7P 453563-05-8P, N-[4-(tert-Butyl)phenyl]-2-fluoropyridine-3-

carboxamide 453563-09-2P, N-(4-tert-Butylphenyl)-2,6-difluoronicotinamide 453563-19-4P 629651-95-2P 629651-96-3P 629651-97-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of 2-aminopyridine-3-carboxamides for treating **angiogenesis** mediated diseases)

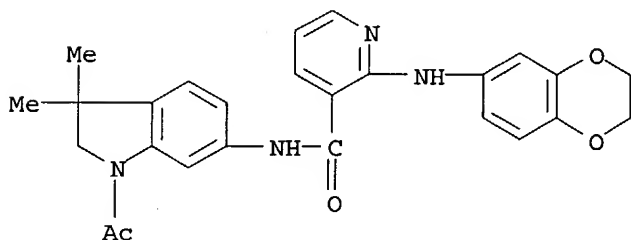
IT 453564-16-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-aminopyridine-3-carboxamides for treating **angiogenesis** mediated diseases)

RN 453564-16-4 HCAPLUS

CN 3-Pyridinecarboxamide, N-(1-acetyl-2,3-dihydro-3,3-dimethyl-1H-indol-6-yl)-2-[(2,3-dihydro-1,4-benzodioxin-6-yl)amino]- (9CI) (CA INDEX NAME)



L108 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2003:855655 HCAPLUS

DN 139:350636

ED Entered STN: 31 Oct 2003

TI Preparation of amino heteroaryl amides for use in pharmaceutical compositions for the treatment of **angiogenesis** mediated diseases such as cancer

IN Patel, Vinod F.; Askew, Benny; Booker, Shon; Chen, Guoqing; Di Pietro, Lucian V.; Germain, Julie; Habgood, Gregory J.; Huang, Qi; Kim, Tae-seong; Li, Aiwen; Nishimura, Nobuko; Nomak, Rana; Riahi, Babak; Yuan, Chester Chenguang; Elbaum, Daniel

PA Amgen Inc., USA

SO U.S. Pat. Appl. Publ., 148 pp., Cont.-in-part of U.S. Ser. No. 46,622. CODEN: USXXCO

DT Patent

LA English

IC ICM C07D043-02

ICS C07D041-02; A61K031-517; A61K031-4439

NCL 514266210; 514338000; 544284000; 546273400; 546277100; 546275700

CC 27-16 (Heterocyclic Compounds (One Hetero Atom))

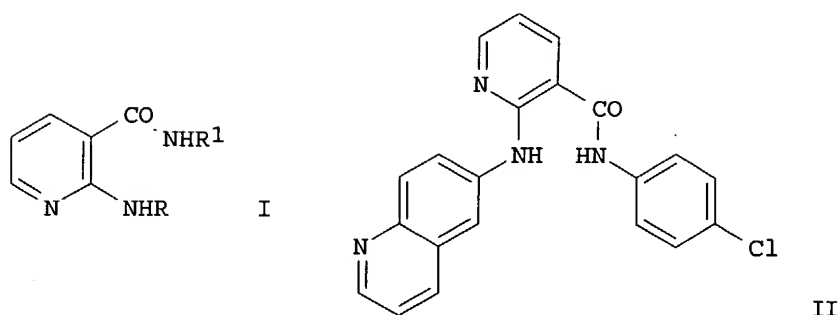
Section cross-reference(s): 1, 28, 31, 63

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003203922	A1	20031030	US 2002-197918	20020717 <--
	US 2003195230	A1	20031016	US 2002-46622	20020110 <--
	WO 2004007481	A2	20040122	WO 2003-US22275	20030715
	WO 2004007481	A3	20040219		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,

PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,  
 UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,  
 TJ, TM  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,  
 CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,  
 NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,  
 GW, ML, MR, NE, SN, TD, TG  
 PRAI US 2001-261882P P 20010112 <--  
 US 2001-323808P P 20010919 <--  
 US 2002-46622 A2 20020110  
 US 2002-197918 A 20020717  
 OS MARPAT 139:350636  
 GI



- AB Amino substituted heteroaryl amides, such as I [R = nitrogen containing heteroaryl, such as quinolinyl, isoquinolinyl, indazolyl; R1 = aryl, cycloalkyl, heteroaryl, heterocyclyl], were prepared for therapeutic use. The invention encompasses novel compds., analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compns. and methods for prophylaxis and treatment of cancer, **angiogenesis** related disorders, KDR-related disorders, cell proliferation related disorders, inflammation, reducing blood flow in tumors, reducing tumor size and diabetic retinopathy. Thus, amide II was prepared via an amination reaction of 2-chloronicotinic acid with 6-aminoquinoline followed by an amidation reaction of the aminonicotinic acid derivative thus formed with 4-chloroaniline. Biol. evaluations included HUVEC proliferation assay, inhibition of **angiogenesis** in the rat corneal **neovascularization** micropocket model, and antitumor activity using A431 rat tumor cells.
- ST heteroaryl amide prepn **angiogenesis** inhibitor; KDR related disorder treatment heteroaryl amide prepn; proliferation related disorder treatment heteroaryl amide prepn; inflammation treatment heteroaryl amide prepn; diabetic retinopathy treatment heteroaryl amide prepn; cancer tumor treatment heteroaryl amide prepn; antitumor agents heteroaryl amide prepn; antiinflammatory agent heteroaryl amide prepn
- IT Gene, animal  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (KDR, disorders; preparation of aminopyridinecarboxamides for therapeutic use in treatment of **angiogenesis** mediated diseases such as cancer)
- IT Eye, disease  
 (diabetic retinopathy, treatment; preparation of aminopyridinecarboxamides for therapeutic use in treatment of **angiogenesis** mediated diseases such as cancer)
- IT **Angiogenesis inhibitors**  
 Anti-inflammatory agents

Antitumor agents

Cytotoxic agents

Human

(preparation of aminopyridinecarboxamides for therapeutic use in treatment of **angiogenesis** mediated diseases such as cancer)

IT Drug delivery systems

(prodrugs; preparation of aminopyridinecarboxamides for therapeutic use in treatment of **angiogenesis** mediated diseases such as cancer)

IT Inflammation

Neoplasm

(treatment; preparation of aminopyridinecarboxamides for therapeutic use in treatment of **angiogenesis** mediated diseases such as cancer)

IT 454480-74-1P 454481-03-9P 454481-08-4P

454481-54-0P 454481-69-7P 454481-80-2P

454481-81-3P 454481-82-4P 618445-79-7P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic

preparation); THU (Therapeutic use); BIOL (Biological study); PREP

(Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of aminopyridinecarboxamides for therapeutic use in treatment of **angiogenesis** mediated diseases such as cancer)

IT 453564-50-6P 454480-67-2P 454480-68-3P

454480-69-4P 454480-70-7P 454480-71-8P

454480-72-9P 454480-73-0P 454480-75-2P

454480-76-3P 454480-77-4P 454480-78-5P

454480-79-6P 454480-80-9P 454480-81-0P

454480-82-1P 454480-83-2P 454480-84-3P

454480-85-4P 454480-86-5P 454480-87-6P

454480-88-7P 454480-89-8P 454480-90-1P

454480-91-2P 454480-92-3P 454480-93-4P

454480-94-5P 454480-95-6P 454480-96-7P

454480-98-9P 454480-99-0P 454481-00-6P

454481-01-7P 454481-02-8P 454481-04-0P

454481-05-1P 454481-06-2P 454481-07-3P

454481-09-5P 454481-10-8P 454481-11-9P

454481-12-0P 454481-13-1P 454481-14-2P

454481-15-3P 454481-16-4P 454481-17-5P

454481-18-6P 454481-19-7P 454481-20-0P

454481-21-1P 454481-22-2P 454481-23-3P

454481-24-4P 454481-25-5P 454481-26-6P

454481-27-7P 454481-28-8P 454481-29-9P

454481-30-2P 454481-31-3P 454481-33-5P

454481-34-6P 454481-35-7P 454481-36-8P

454481-37-9P 454481-38-0P 454481-39-1P

454481-41-5P 454481-42-6P 454481-43-7P

454481-44-8P 454481-45-9P 454481-46-0P

454481-47-1P 454481-48-2P 454481-49-3P

454481-50-6P 454481-51-7P 454481-52-8P

454481-53-9P 454481-55-1P 454481-56-2P

454481-57-3P 454481-58-4P 454481-59-5P

454481-60-8P 454481-61-9P 454481-62-0P

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454481-66-4P 454481-67-5P 454481-68-6P

454481-70-0P 454481-71-1P 454481-72-2P

454481-73-3P 454481-74-4P 454481-75-5P

454481-76-6P 454481-77-7P 454481-78-8P

454481-79-9P 454481-83-5P 454481-84-6P

454481-86-8P 454481-87-9P 454481-88-0P

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454481-92-6P 454481-93-7P 454481-94-8P

454481-95-9P 454481-96-0P 454481-97-1P

454482-02-1P 454482-03-2P 454482-04-3P

618445-28-6P 618445-29-7P 618445-30-0P

618445-31-1P 618445-32-2P 618445-33-3P

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 618445-67-3P 618445-68-4P 618445-69-5P  
 618445-70-8P 618445-71-9P 618445-72-0P  
 618445-73-1P 618445-74-2P 618445-75-3P  
 618445-76-4P 618445-77-5P 618445-78-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
 (Uses)

(preparation of aminopyridinecarboxamides for therapeutic use in treatment  
 of angiogenesis mediated diseases such as cancer)

IT 51-75-2, Bis(2-chloroethyl)methylamine 55-86-7, Methyl-bis-(2-  
 chloroethyl)amine hydrochloride 70-34-8, 2,4-Dinitrofluorobenzene  
 75-03-6, Iodoethane 75-89-8, 2,2,2-Trifluoroethanol 99-57-0,  
 2-Amino-4-nitrophenol 99-88-7, 4-Isopropylaniline 102-28-3,  
 3'-Aminoacetanilide 105-67-9, 2,4-Dimethylphenol 106-47-8,  
 4-Chloroaniline, reactions 106-52-5, 4-Hydroxy-N-methylpiperidine  
 108-01-0, N,N-Dimethylethanolamine 109-01-3, N-Methylpiperazine  
 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions  
 111-77-3, 2-(2-Methoxyethoxy)ethan-1-ol 123-00-2, 4-(3-  
 Aminopropyl)morpholine 123-75-1, Pyrrolidine, reactions 139-59-3,  
 4-Phenoxyaniline 271-63-6, 1H-Pyrrolo[2,3-b]pyridine 328-79-0,  
 1-Methoxy-3-nitro-5-trifluoromethylbenzene 328-80-3 360-54-3, Methyl  
 2-(trifluoromethyl)-3,3,3-trifluoropropionate 372-47-4, 3-Fluoropyridine  
 372-48-5, 2-Fluoropyridine 401-99-0, 3,5-Dinitrobenzotrifluoride  
 536-33-4 555-21-5, 4-Nitrophenylacetone nitrile 555-68-0, 3-Nitrocinnamic  
 acid 580-15-4, 6-Aminoquinoline 598-21-0, Bromoacetyl bromide  
 619-17-0, 2-Amino-4-nitrobenzoic acid 624-28-2, 2,5-Dibromopyridine  
 643-43-6, (2,4-Dinitrophenyl)acetic acid 722-92-9, 4-[2,2,2-Trifluoro-1-  
 hydroxy-1-(trifluoromethyl)ethyl]phenylamine 769-92-6,  
 4-tert-Butylaniline 814-68-6, Acryloyl chloride 1068-57-1, Acetic acid  
 hydrazide 1083-48-3, 4-(4-Nitrobenzyl)pyridine 1118-68-9,  
 Dimethylaminoacetic acid 1126-09-6, Piperidine-4-carboxylic acid ethyl  
 ester 1202-00-2, [2-(2-Aminophenoxy)ethyl]dimethylamine 1445-73-4,  
 1-Methyl-4-piperidone 1458-98-6, 3-Bromo-2-methylpropene 1692-15-5,  
 4-Pyridylboronic acid 2008-75-5, 1-(2-Chloroethyl)piperidine  
 monohydrochloride 2314-97-8, Trifluoromethyl iodide 2393-23-9,  
 4-Methoxybenzylamine 2402-67-7 2942-59-8, 2-Chloronicotinic acid  
 3240-94-6, 4-(2-Chloroethyl)morpholine 3279-07-0, 2-Nitro-4-tert-  
 butylphenol 3282-56-2, 1-(tert-Butyl)-4-nitrobenzene 3350-78-5,  
 3,3-Dimethylacryloyl chloride 3389-21-7, 3-(2-Bromoethyl)-1H-indole  
 3438-46-8, 4-Methylpyrimidine 3731-53-1, Pyridin-4-ylmethylamine  
 4009-98-7, Methoxymethyltriphenylphosphonium chloride 4160-54-7,  
 1,3-Dinitro-4-tert-butylbenzene 4637-24-5, Dimethylformamide dimethyl  
 acetal 4769-96-4, 6-Nitroindole 4920-79-0, 2-Chloro-4-nitroanisole  
 5332-96-7, 1-(4-Nitrophenyl)propan-2-one 5458-84-4, 2-Iodo-5-  
 nitroanisole 5600-21-5, 2-Amino-4-chloro-6-methylpyrimidine 6146-52-7,  
 5-Nitroindole 6310-21-0, 2-tert-Butylaniline 6313-33-3, Formamidine  
 monohydrochloride 6967-12-0, 6-Aminoindazole 7223-38-3,  
 1-Dimethylamino-2-propyne 7364-33-2 7597-18-4, 6-Nitroindazole  
 10403-47-1, 2-Bromo-5-nitroaniline 14446-67-4, 1-Allylpiperidine  
 19727-83-4, 6-Nitroindoline 19798-81-3, 2-Amino-6-bromopyridine  
 19910-33-9, 2-(4-Nitrophenyl)propionic acid 20769-85-1,  
 2-Bromo-2-methylpropionyl bromide 22245-96-1 33252-30-1,

2-Chloro-4-cyanopyridine 33786-89-9, 5-Chlorobenzene-1,3-diamine  
 49609-84-9, 2-Chloronicotinoyl chloride 49844-90-8, 4-Chloro-2-  
 methylsulfanylpurimidine 51149-08-7, 3,6-Dichloropyridazine-4-carboxylic  
 acid 51304-58-6 53062-99-0 54962-75-3, 3-Bromo-5-  
 (trifluoromethyl)phenylamine 57260-71-6, N-Boc-piperazine 59382-59-1,  
 Methyl 2-methyl-3-nitro benzoate 70987-78-9 73183-34-3 75833-38-4,  
 2-Chloropyrimidine-4-carbonitrile 79099-07-3 80887-01-0,  
 2-Bromo-5-nitrobenzoyl chloride 86087-23-2 97628-92-7 99724-19-3  
 102362-98-1, 3,3-Dimethyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide  
 109384-19-2, 1-Boc-4-hydroxypiperidine 110073-17-1, Methyl  
 2-morpholin-4-ylpropionate 110763-09-2 123855-51-6 132873-57-5  
 142253-55-2 148546-99-0, 1-(3-Aminophenyl)-4-methylpiperazine  
 170491-63-1 171178-50-0, 2,6-Difluoropyridine-3-carboxylic acid  
 183946-06-7, 2-Methyl-4-nitro-1-pentafluoroethylbenzene 196932-95-3  
 230299-53-3 442846-90-4 453560-55-9, 1-Boc-2-(3-nitro-5-  
 trifluoromethylphenoxy)methylpyrrolidine 453560-61-7,  
 3,3-Dimethyl-1-(1-Boc-piperidin-4-ylmethyl)-6-nitro-2,3-dihydro-1H-indole  
 453560-64-0, 2-Methoxy-4-nitro-1-pentafluoroethylbenzene 453560-68-4  
 453560-72-0, (S)-2-Chloro-N-[4-(2-oxiran-2-ylmethoxy)]-3-  
 pentafluoroethylphenyl]nicotinamide 453560-93-5, 1-Methyl-4-[1-methyl-1-  
 (4-nitrophenyl)ethyl]pyridinium 454482-16-7 454482-17-8 618445-84-4  
 618445-90-2 618445-95-7 618445-98-0 618446-13-2 618446-23-4  
 618446-48-3 618446-51-8

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of aminopyridinecarboxamides for therapeutic use in treatment  
 of **angiogenesis** mediated diseases such as cancer)

IT 174-66-3P 349-57-5P, 3-Nitro-5-trifluoromethylphenol 393-55-5P,  
 2-Fluoropyridine-3-carboxylic acid 401-94-5P 619-10-3P,  
 2-Chloro-5-nitrophenol 695-37-4P, 3-Fluoropyridine 1-oxide 771-99-3P,  
 4-Phenylpiperidine 774-52-7P, 1-Methyl-4-phenylpiperidine 1073-65-0P,  
 Pyrimidine-4-carboxaldehyde oxime 6310-17-4P 6850-23-3P 6943-17-5P  
 10043-37-5P 13209-80-8P 13669-28-8P, 1-Methyl-4-methylenepiperidine  
 17329-31-6P, 6-Amino-3H-quinazolin-4-one 20364-31-2P 20691-89-8P,  
 (1-Methylpiperidin-4-yl)methanol 24252-37-7P, 1-Methylpiperidine-4-  
 carboxylic acid ethyl ester 28286-03-5P 31930-18-4P 40919-12-8P  
 42182-27-4P 54815-23-5P, 2-(4-Aminophenyl)-2-methylpropionic acid methyl  
 ester 55052-24-9P, 1H-Pyrrolo[2,3-b]pyridine 7-oxide 55052-28-3P,  
 4-Chloro-1H-pyrrolo[2,3-b]pyridine 56149-31-6P 57841-51-7P  
 58021-55-9P 58605-12-2P 59115-08-1P, 2-Methyl-2-(4-  
 nitrophenyl)propionic acid methyl ester 59182-61-5P 69296-06-6P,  
 2-Morpholin-4-ylpropanol 70564-16-8P, 2-Ethyl-4-aminomethylpyridine  
 72716-86-0P, 4-Cyano-2-methoxypyridine 74728-65-7P, 1-Methyl-6-amino-1H-  
 indazole 76693-04-4P, 4,4-Dimethyl-3,4-dihydro-1H-quinolin-2-one  
 85160-84-5P, 2,2-Dimethyl-6-nitro-4H-benzo[1,4]oxazin-3-one 90221-50-4P,  
 N-(2-Bromo-5-nitrophenyl)acetamide 91133-58-3P 97483-77-7P,  
 5-Bromopyridine-2-carbonitrile 97509-75-6P 98475-07-1P 103392-84-3P,  
 2-tert-Butyl-5-nitroaniline 103394-70-3P, 4-tert-Butyl-3-  
 nitrophenylamine 105807-77-0P, 2,2,4-Trimethyl-6-nitro-4H-  
 benzo[1,4]oxazin-3-one 105807-84-9P, 6-Amino-2,2-dimethyl-4H-  
 benzo[1,4]oxazin-3-one 106516-27-2P, 3-(1-Methyl-1,2,3,6-  
 tetrahydropyridin-4-yl)-5-nitro-1H-indole 111080-65-0P 111080-66-1P  
 111196-85-1P, 2-Methyl-2-(4-nitrophenyl)propionic acid 114262-65-6P,  
 4-(1,1,2,2,3,3,4,4,4-Nonafluorobutyl)phenylamine 117242-06-5P,  
 4,4-Dimethyl-7-nitro-3,4-dihydro-2H-isoquinolin-1-one 119899-26-2P,  
 2-Fluoropyridine-3-carbonyl chloride 125089-58-9P 125089-59-0P  
 126099-59-0P 136545-11-4P, 2,2-Dimethyl-6-nitro-3,4-dihydro-2H-  
 benzo[1,4]oxazine 137076-22-3P, 1-Boc-4-formylpiperidine 137225-13-9P  
 140837-70-3P, 3,3-Dimethyl-6-nitro-2,3-dihydrobenzo[d]isothiazole  
 1,1-dioxide 141699-58-3P 142253-56-3P, 1-Boc-3-Hydroxymethylazetidine  
 142851-03-4P, 1-Boc-Piperidine-4-carboxylic acid ethyl ester  
 144293-82-3P, 1-(2,2-Dimethyl-6-nitro-2,3-dihydrobenzo[1,4]oxazin-4-  
 yl)ethanone 144293-83-4P, 1-(6-Amino-2,2-dimethyl-2,3-  
 dihydrobenzo[1,4]oxazin-4-yl)ethanone 148900-69-0P, (2-Methoxypyridin-4-

yl)methylamine 149532-90-1P, (2-Methoxypyridin-4-yl)methylamine  
hydrochloride 150544-04-0P 160726-81-8P 161975-39-9P,  
1-Boc-4-Methylsulfonyloxymethylpiperidine 173094-82-1P,  
2-(1H-Indazol-6-ylamino)pyridine-3-carboxylic acid 177947-88-5P  
179898-72-7P 180692-27-7P, Trifluoromethanesulfonic acid  
1-Methyl-1,2,3,6-tetrahydropyridin-4-yl ester 181363-19-9P  
182564-38-1P 199296-51-0P 312904-51-1P 327056-62-2P 366452-97-3P  
366452-98-4P 408328-42-7P 442846-54-0P, [2-(1-Methylpiperidin-4-  
yloxy)pyridin-4-yl]methylamine 442846-55-1P, [2-(1-Methylpyrrolidin-2-  
ylmethoxy)pyridin-4-yl]methylamine 442846-56-2P, (4-Aminomethylpyridin-2-  
yl)(3-morpholin-4-ylpropyl)amine 442846-58-4P, [2-(1-Methylpiperidin-4-  
ylmethoxy)pyridin-4-yl]methylamine 442846-59-5P, 3-(4-Boc-piperazin-1-  
ylmethyl)-5-trifluoromethylphenylamine 442846-60-8P,  
3-(4-Methylpiperazin-1-ylmethyl)-4-pentafluoroethylphenylamine  
442846-61-9P, 7-Amino-2-(4-methoxybenzyl)-4,4-dimethyl-3,4-dihydro-2H-  
isoquinolin-1-one 442846-62-0P, (3-Amino-5-trifluoromethylphenyl)(4-Boc-  
piperazin-1-yl)methanone 442846-63-1P, 1-(7-Amino-4,4-dimethyl-3,4-  
dihydro-1H-isoquinolin-2-yl)ethanone 442846-64-2P, 4-tert-Butyl-3-(1-Boc-  
pyrrolidin-3-ylmethoxy)phenylamine 442846-65-3P, 4-tert-Butyl-3-(1-Boc-  
azetidin-3-ylmethoxy)phenylamine 442846-67-5P, N-(4-Acetyl-2,2-dimethyl-  
3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-fluoronicotinamide 442846-68-6P,  
2-Fluoro-N-(2,2,4-trimethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-  
yl)nicotinamide 442846-69-7P, N-(2,2-Dimethyl-3-oxo-3,4-dihydro-2H-  
benzo[1,4]oxazin-6-yl)-2-fluoronicotinamide 442846-70-0P,  
2-Fluoro-N-[3-(4-methylpiperazin-1-ylmethyl)-5-  
trifluoromethylphenyl]nicotinamide 442846-71-1P, 2-Fluoro-N-(2-Boc-4,4-  
dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)nicotinamide 442846-72-2P,  
2-Fluoro-N-[3-(4-methylpiperazin-1-ylmethyl)-4-  
pentafluoroethylphenyl]nicotinamide 442846-73-3P, 2-Fluoro-N-(4,4-  
dimethyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)nicotinamide  
442846-74-4P 442846-75-5P, 2-Fluoro-N-[3-(4-Boc-piperazin-1-ylmethyl)-5-  
trifluoromethylphenyl]nicotinamide 442846-76-6P, N-(2-Acetyl-4,4-  
dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-fluoronicotinamide  
442846-77-7P, N-[3,3-Dimethyl-1-(1-methylpiperidin-4-yl)-2,3-dihydro-1H-  
indol-6-yl]-2-fluoronicotinamide 442846-78-8P, 2-Fluoro-N-[3-(1-Boc-  
azetidin-3-ylmethoxy)-5-trifluoromethylphenyl]nicotinamide 442846-79-9P,  
(S)-N-[4-tert-Butyl-3-(1-Boc-pyrrolidin-2-ylmethoxy)phenyl]-2-  
fluoronicotinamide 442846-80-2P, 2-Chloro-N-[2-(4-methoxybenzyl)-4,4-  
dimethyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]nicotinamide  
442846-81-3P, 2-Chloro-N-(4,4-dimethyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-  
7-yl)nicotinamide 442846-82-4P, 2-[3-[(2-Chloropyridine-3-  
carbonyl)amino]phenyl]-2-methylpropionic acid methyl ester 442846-83-5P,  
N-[4-tert-Butyl-3-[2-(1-Boc-piperidin-4-yl)ethyl]phenyl]-2-  
chloronicotinamide 442846-84-6P 442846-85-7P 442846-86-8P  
442846-87-9P 442846-88-0P, 1-[2-(2-tert-Butyl-5-  
nitrophenoxy)ethyl]piperidine 442846-89-1P, 3,3-Dimethyl-1-(1-  
methylpiperidin-4-yl)-6-nitro-2,3-dihydro-1H-indole 442846-91-5P,  
1-(4,4-Dimethyl-7-nitro-3,4-dihydro-1H-isoquinolin-2-yl)ethanone  
442846-92-6P, 2-Bromo-N-(4-methoxybenzyl)-5-nitrobenzamide 442846-93-7P,  
4,4-Dimethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline 442846-94-8P,  
1-Boc-4-(3-nitro-5-trifluoromethylbenzyl)piperazine 442846-96-0P  
442846-97-1P, 1-Methyl-4-[1-methyl-1-(4-nitrophenyl)ethyl]pyridinium  
iodide 442846-98-2P, 1-Methyl-4-(4-nitrobenzyl)-1,2,3,6-  
tetrahydropyridine 442846-99-3P 442847-02-1P 442847-03-2P  
442847-04-3P, [3-[3-Amino-5-(trifluoromethyl)phenyl]propyl]dimethylamine  
442847-06-5P, 4-(2-tert-Butyl-5-nitrophenyl)pyridine 442847-08-7P,  
4-tert-Butyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)aniline  
442847-11-2P, -2-tert-Butyl-5-nitrophenol 443729-67-7P 452929-03-2P,  
1-(2-tert-Butylphenyl)-4-methylpiperazine 453560-49-1P,  
1-Boc-4-(3-nitro-5-trifluoromethylphenoxy)piperidine 453560-50-4P,  
1-Boc-4-(3-amino-5-trifluoromethylphenoxy)piperidine 453560-51-5P,  
(S)-4-tert-Butyl-3-(1-Boc-pyrrolidin-2-ylmethoxy)phenylamine  
453560-52-6P 453560-54-8P, 2-(3-Nitro-5-trifluoromethylphenoxy)methylpyr

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RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of aminopyridinecarboxamides for therapeutic use in treatment of **angiogenesis** mediated diseases such as cancer)

IT 618446-11-0P 618446-12-1P 618446-14-3P 618446-15-4P 618446-16-5P 618446-17-6P 618446-18-7P 618446-19-8P 618446-20-1P 618446-21-2P 618446-22-3P 618446-24-5P 618446-25-6P 618446-26-7P 618446-27-8P 618446-28-9P 618446-29-0P 618446-30-3P, 2-(2,2,2-Trifluoroethoxy)isonicotinonitrile 618446-31-4P 618446-32-5P 618446-33-6P 618446-34-7P 618446-35-8P 618446-36-9P 618446-37-0P 618446-38-1P 618446-39-2P 618446-40-5P 618446-41-6P 618446-42-7P 618446-43-8P 618446-44-9P 618446-45-0P 618446-46-1P 618446-47-2P 618446-49-4P 618446-50-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of aminopyridinecarboxamides for therapeutic use in treatment of **angiogenesis** mediated diseases such as cancer)

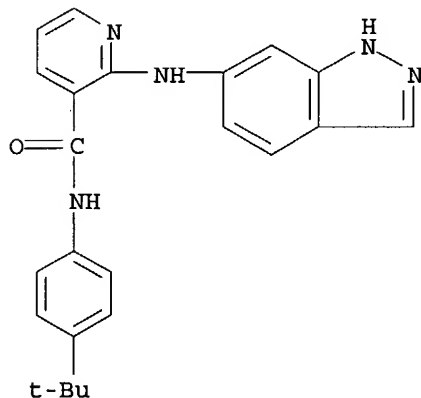
IT 454480-74-1P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of aminopyridinecarboxamides for therapeutic use in treatment of angiogenesis mediated diseases such as cancer)

RN 454480-74-1 HCAPLUS

CN 3-Pyridinecarboxamide, N-[4-(1,1-dimethylethyl)phenyl]-2-(1H-indazol-6-ylamino)- (9CI) (CA INDEX NAME)



L108 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2003:551181 HCAPLUS

DN 139:117339

ED Entered STN: 18 Jul 2003

TI Preparation of substituted arylamine derivatives as antitumor agents

IN Elbaum, Daniel; Askew, Benny; Booker, Shon; Germain, Julie; Habgood, Gregory; Handley, Michael; Kim, Tae-Seong; Li, Aiwen; Nishimura, Nobuko; Patel, Vinod F.; Yuan, Chester Chenguang; Kim, Joseph L.

PA Amgen Inc., USA

SO U.S. Pat. Appl. Publ., 106 pp., Cont.-in-part of U.S. Ser. No. 46,526.  
CODEN: USXXCO

DT Patent

LA English

IC ICM C07D417-02

ICS C07D413-02; C07D043-02; C07D041-02; A61K031-55; A61K031-541; A61K031-5377; A61K031-496; A61K031-4439; A61K031-4545

NCL 514210200; 514217040; 514227800; 514235500; 514253130; 514318000; 514336000; 540597000; 544060000; 546268100

CC 27-16 (Heterocyclic Compounds (One Hetero Atom))

Section cross-reference(s): 1, 63

FAN.CNT 2

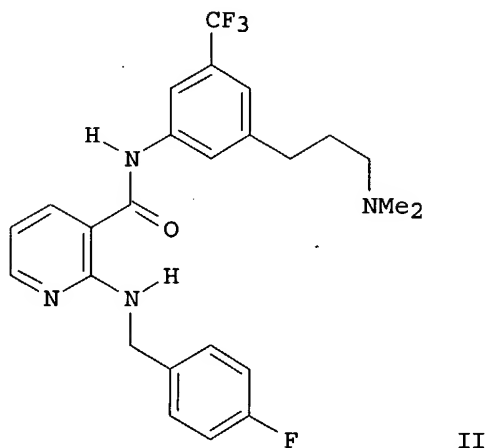
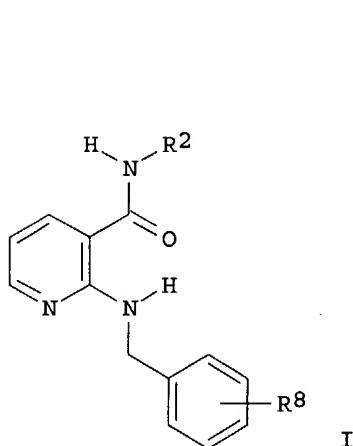
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003134836	A1	20030717	US 2002-197960	20020717 <--
US 2002147198	A1	20021010	US 2002-46526	20020110 <--
WO 2004007457	A2	20040122	WO 2003-US22276	20030715

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,

CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,  
 NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,  
 GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-261360P P 20010112 <--  
 US 2001-323686P P 20010919  
 US 2002-46526 A2 20020110  
 US 2002-197960 A 20020717  
 OS MARPAT 139:117339  
 GI



- AB The title compds. I [R2 = (un)substituted Ph, 9-10 membered bicyclic and 11-14 membered tricyclic (un)saturated heterocyclyl; R8 = halo, NH2, NO2, etc.], and their pharmaceutically acceptable derivs., are prepared and disclosed as agents effective for prophylaxis and treatment of diseases, such as **angiogenesis** mediated diseases. E.g., a multi-step synthesis of II, starting from 1-dimethylamino-2-propyne and 3-bromo-5-trifluoromethylaniline, was given. Selected compds. of the invention, e.g., II, inhibited VEGF-stimulated cell proliferation at a level below 50 nM. The invention encompasses novel compds., analogs, prodrugs and pharmaceutically acceptable derivs. thereof, pharmaceutical compns. and methods for prophylaxis and treatment of diseases and other maladies or conditions involving, cancer and the like.
- ST arylamine prepn antitumor **angiogenesis** inhibitor;  
 pyridinecarboxamide amino prepn antitumor VEGF inhibitor
- IT Cytotoxic agents  
 (antimetabolites; preparation of substituted aminopyridines for treating cancer in combination with other agents)
- IT Eye, disease  
 (diabetic retinopathy, treatment of; preparation of substituted aminopyridines as antitumor agents)
- IT Hormones, animal, biological studies  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (hormone-type agents; preparation of substituted aminopyridines for treating cancer in combination with other agents)
- IT Interferons  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (interferon-type agents; preparation of substituted aminopyridines for treating cancer in combination with other agents)
- IT **Angiogenesis**  
**Angiogenesis inhibitors**  
 Antitumor agents  
 Human  
 Neoplasm

(preparation of substituted aminopyridines as antitumor agents)

IT Alkylating agents, biological  
Antibiotics  
Immunomodulators  
(preparation of substituted aminopyridines for treating cancer in combination with other agents)

IT Cell proliferation  
(treatment of related disorders; preparation of substituted aminopyridines as antitumor agents)

IT Vascular endothelial growth factor receptors  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(type VEGFR-2, treatment of related disorders; preparation of substituted aminopyridines as antitumor agents)

IT 393-55-5P 6310-17-4P 20691-89-8P 54815-23-5P 105807-84-9P  
144293-82-3P 179898-72-7P 180692-27-7P 375853-85-3P 442846-54-0P  
442846-55-1P 442846-56-2P 442846-57-3P 442846-58-4P 442846-59-5P  
442846-60-8P 442846-61-9P 442846-62-0P 442846-63-1P 442846-64-2P  
442846-65-3P 442846-66-4P 442846-67-5P 442846-68-6P 442846-69-7P  
442846-70-0P 442846-71-1P 442846-72-2P 442846-73-3P 442846-74-4P  
442846-75-5P 442846-76-6P 442846-77-7P 442846-78-8P 442846-79-9P  
442846-80-2P 442846-81-3P 442846-82-4P 442846-83-5P 442846-84-6P  
442846-85-7P 442846-86-8P 442846-87-9P 442846-88-0P 442846-89-1P  
442846-90-4P 442846-91-5P 442846-92-6P 442846-93-7P 442846-94-8P  
442846-95-9P 442846-96-0P 442846-97-1P 442846-98-2P 442846-99-3P  
442847-00-9P 442847-01-0P 442847-02-1P 442847-03-2P 442847-04-3P  
442847-05-4P 442847-06-5P 442847-07-6P 442847-08-7P 442847-09-8P  
442847-10-1P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(intermediate; preparation of substituted aminopyridines as antitumor agents)

IT 561297-65-2P 561297-67-4P  
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(preparation of substituted aminopyridines as antitumor agents)

IT 561297-60-7P 561297-61-8P 561297-62-9P 561297-63-0P 561297-64-1P  
561297-66-3P 561297-68-5P 561297-69-6P 561297-70-9P 561297-71-0P  
561297-72-1P 561298-02-0P 561298-03-1P  
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of substituted aminopyridines as antitumor agents)

IT 75-89-8, 2,2,2-Trifluoroethanol 100-52-7, Benzaldehyde, reactions  
100-82-3, 3-Fluorobenzylamine 102-28-3, 3'-Aminoacetanilide 106-47-8,  
4-Chloroaniline, reactions 106-52-5, 4-Hydroxy-1-methylpiperidine  
111-77-3 123-75-1, Pyrrolidine, reactions 139-59-3, 4-Phenoxyaniline  
140-75-0, 4-Fluorobenzylamine 372-47-4, 3-Fluoropyridine 372-48-5,  
2-Fluoropyridine 456-64-4 555-21-5, 4-Nitrophenylacetonitrile  
624-28-2, 2,5-Dibromopyridine 722-92-9 769-92-6, 4-tert-Butylaniline  
1083-48-3, 4-(4-Nitrobenzyl)pyridine 1445-73-4, 1-Methyl-piperidin-4-one  
1458-98-6, 3-Bromo-2-methylpropene 1462-86-8, 3-Aminopicolinic acid  
1692-15-5, 4-Pyridylboronic acid 2008-75-5, 1-(2-Chloroethyl)piperidine  
hydrochloride 2393-23-9, 4-Methoxybenzylamine 2620-50-0,  
1,3-Benzodioxole-5-methanamine 3282-56-2 3350-78-5,  
3,3-Dimethylacryloyl chloride 3554-65-2 4535-90-4 4920-79-0,  
2-Chloro-4-nitroanisole 5332-96-7, 1-(4-Nitrophenyl)propan-2-one  
5600-21-5, 2-Amino-4-chloro-6-methylpyrimidine 6146-52-7, 5-Nitroindole  
6310-21-0, 2-tert-Butylaniline 6313-33-3, Formamidinium hydrochloride  
7223-38-3, 1-Dimethylamino-2-propyne 10403-47-1, 2-Bromo-5-nitroaniline  
19727-83-4, 6-Nitroindoline 19910-33-9, 2-(4-Nitrophenyl)propionic acid  
33252-30-1, 2-Chloro-4-cyanopyridine 49609-84-9, 2-Chloropyridine-3-  
carbonyl chloride 51149-08-7, 3,6-Dichloropyridazine-4-carboxylic acid

54962-75-3, 3-Bromo-5-trifluoromethylaniline 59115-08-1 59382-59-1,  
Methyl 2-methyl-3-nitrobenzoate 80887-01-0, 2-Bromo-5-nitrobenzoyl  
chloride 117242-06-5 132873-57-5 137076-22-3, N-tert-Butoxycarbonyl-  
4-formylpiperidine 142253-57-4 202865-68-7, 3-Bromo-4-  
fluorobenzylamine hydrochloride 442847-11-2 442847-12-3 442847-13-4  
442847-14-5 442847-15-6 442847-16-7 442847-17-8 442847-18-9  
442847-19-0 442847-20-3 442847-21-4 442847-22-5 453560-94-6  
561298-00-8 561298-01-9

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of substituted aminopyridines as antitumor agents)

IT 695-37-4P 3276-37-7P 13209-80-8P 20364-31-2P 90221-50-4P  
97509-75-6P 106516-27-2P 125089-58-9P 125089-59-0P 126099-59-0P  
137225-13-9P 182564-38-1P 255060-77-6P 312904-51-1P 366452-97-3P  
366452-98-4P 453560-61-7P 453560-88-8P 453562-54-4P 453562-59-9P  
453562-60-2P 453562-67-9P 453562-68-0P 453562-71-5P 454482-06-5P  
454482-07-6P 561297-73-2P 561297-74-3P 561297-75-4P 561297-76-5P  
561297-77-6P 561297-78-7P 561297-79-8P 561297-80-1P 561297-81-2P  
561297-82-3P 561297-83-4P 561297-84-5P 561297-85-6P 561297-86-7P  
561297-87-8P 561297-88-9P 561297-89-0P 561297-90-3P 561297-91-4P  
561297-93-6P 561297-96-9P 561297-97-0P 561297-98-1P 561297-99-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)

(preparation of substituted aminopyridines as antitumor agents)

IT 442845-74-1P 442845-77-4P 442846-13-1P 442846-17-5P 442846-22-2P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic  
preparation); THU (Therapeutic use); BIOL (Biological study); PREP  
(Preparation); RACT (Reactant or reagent); USES (Uses)

(target compound; preparation of substituted aminopyridines as antitumor  
agents)

IT 442845-71-8P 442845-72-9P 442845-73-0P 442845-75-2P 442845-76-3P  
442845-78-5P 442845-79-6P 442845-80-9P 442845-81-0P 442845-82-1P  
442845-83-2P 442845-84-3P 442845-85-4P 442845-86-5P 442845-87-6P  
442845-88-7P 442845-89-8P 442845-90-1P 442845-91-2P 442845-92-3P  
442845-93-4P 442845-94-5P 442845-95-6P 442845-96-7P 442845-97-8P  
442845-98-9P 442845-99-0P 442846-00-6P 442846-01-7P 442846-02-8P  
442846-03-9P 442846-04-0P 442846-05-1P 442846-06-2P 442846-07-3P  
442846-08-4P 442846-09-5P 442846-10-8P 442846-11-9P 442846-12-0P  
442846-14-2P 442846-15-3P 442846-16-4P 442846-18-6P 442846-19-7P  
442846-20-0P 442846-21-1P 442846-23-3P 442846-24-4P 442846-25-5P  
442846-26-6P 442846-27-7P 442846-28-8P 442846-29-9P 442846-30-2P  
442846-31-3P 442846-32-4P 442846-33-5P 442846-34-6P 442846-35-7P  
442846-36-8P 442846-37-9P 442846-38-0P 442846-39-1P 442846-40-4P  
442846-42-6P 442846-44-8P 442847-23-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
(Uses)

(target compound; preparation of substituted aminopyridines as antitumor  
agents)

IT 561298-02-0P

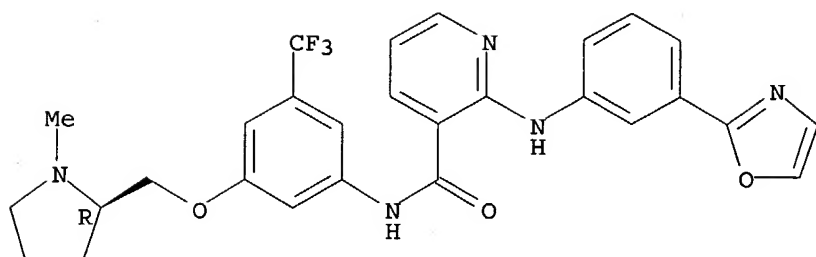
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
(Uses)

(preparation of substituted aminopyridines as antitumor agents)

RN 561298-02-0 HCAPLUS

CN 3-Pyridinecarboxamide, N-[3-[[[(2R)-1-methyl-2-pyrrolidinyl]methoxy]-5-  
(trifluoromethyl)phenyl]-2-[[3-(2-oxazolyl)phenyl]amino]- (9CI) (CA INDEX  
NAME)

Absolute stereochemistry.



L108 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2003:396459 HCAPLUS

DN 138:401732

ED Entered STN: 23 May 2003

TI Preparation of aminothiadiazoles as antiproliferatives.

IN Zhang, Zaihui; Chopiuk, Gregory B.; Daynard, Timothy S.; Wang, Shisen

PA Can.

SO U.S. Pat. Appl. Publ., 27 pp., Cont.-in-part of U.S. 6,420,400.

CODEN: USXXCO

DT Patent

LA English

IC ICM A61K031-433

ICS C07D285-14; C07D417-02

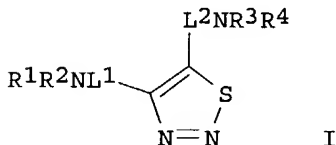
NCL 514361000; 548127000

CC 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003096848	A1	20030522	US 2002-144203	20020510 <--
	US 6420400	B1	20020716	US 2000-545237	20000407 <--
PRAI	US 2000-545237	A2	20000407	<--	
OS	MARPAT 138:401732				
GI					



AB Title compds. [I; R1-R4 = H, R5, R6, R7; R5 = alkyl, heteroalkyl, aryl, heteroaryl; R6 = (R5)n-alkylene, (R5)n-heteroalkylene, (R5)n-arylene, (R5)n-heteroarylene; R7 = (R6)n-alkylene, (R6)n-heteroalkylene, (R6)n-arylene, (R6)n-heteroarylene; n 0-5; R1R2N, R3R4N = heterocyclyl; L1, L2 = A1A2A3; A1, A2, A3 = bond, alkylene, heteroalkylene, arylene, heteroarylene], were prepared. Thus, Me3COK in THF under ice cooling was treated with acetoacetamide and then with PhNCS followed by stirring for 2 h to give a residue which in EtOH was treated with Et3N and then p-tosyl azide followed by stirring for 30 min. at 45° to give 64% 5-phenylamino-1,2,3-thiadiazole-4-carboxamide (KP-15807). The latter at 10 µM in IEC-18 cells reduced cell invasion from 16.8% (controls) to 8%.

ST aminothiadiazoles prepn antiproliferative; hyperproliferation treatment aminothiadiazoles prepn; cell migration inhibitor aminothiadiazoles prepn; apoptosis stimulator aminothiadiazoles prepn; neointimal hyperplasia treatment aminothiadiazoles prepn; angiogenesis inhibitor

aminothiadiazole prepn; lymphoproliferative disorder treatment  
aminothiadiazole prepn

IT Neoplasm  
(cell growth inhibitors; preparation of aminothiadiazoles as antiproliferatives)

IT Apoptosis  
(inducers; preparation of aminothiadiazoles as antiproliferatives)

IT Cell migration  
(inhibitors; preparation of aminothiadiazoles as antiproliferatives)

IT Artery, disease  
(intima, hyperplasia, treatment; preparation of aminothiadiazoles as antiproliferatives)

IT **Angiogenesis inhibitors**  
Antitumor agents  
Human  
(preparation of aminothiadiazoles as antiproliferatives)

IT Lymphoproliferative disorders  
(treatment; preparation of aminothiadiazoles as antiproliferatives)

IT 2039-15-8P 117971-50-3P 149443-19-6P 369605-02-7P 442660-83-5P  
442660-90-4P 442660-91-5P 442660-92-6P 442661-23-6P 528855-39-2P  
**528855-40-5P 528855-41-6P** 528855-42-7P 528855-43-8P  
528855-44-9P 528855-45-0P 528855-46-1P 528855-47-2P 528855-48-3P  
528855-49-4P 528855-50-7P 528855-51-8P 528855-52-9P 528855-53-0P  
528855-54-1P 528855-55-2P 528855-56-3P 528855-57-4P 528855-58-5P  
528855-61-0P 528855-62-1P 528855-63-2P 528855-64-3P 528855-65-4P  
528855-66-5P 528855-67-6P  
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
(Uses)  
(preparation of aminothiadiazoles as antiproliferatives)

IT 103-72-0, Phenyl isothiocyanate 112-71-0, 1-Bromotetradecane 141-78-6,  
Ethyl acetate, reactions 615-20-3, 2-Chlorobenzothiazole 622-59-3,  
4-Methylphenyl isothiocyanate 1544-68-9, 4-Fluorophenyl isothiocyanate  
1645-65-4, 4-Trifluoromethylphenyl isothiocyanate 2038-03-1,  
N-(2-Aminoethyl)morpholine 2131-57-9, 4-Acetylphenyl isothiocyanate  
2131-61-5, 4-Nitrophenyl isothiocyanate 3125-64-2, 3-Methoxyphenyl  
isothiocyanate 3460-49-9, 4-Ethoxyphenyl isothiocyanate 4319-49-7,  
N-Aminomorpholine 5977-14-0, Acetoacetamide 6590-93-8,  
3,5-Dichlorophenyl isothiocyanate 6590-94-9, 3,4-Dichlorophenyl  
isothiocyanate 6590-96-1, 2,4-Dichlorophenyl isothiocyanate 6590-97-2,  
2,3-Dichlorophenyl isothiocyanate 7612-96-6, 4-Phenylazophenyl  
isothiocyanate 15863-41-9, 4-Methylthiophenyl isothiocyanate  
33904-04-0, 3,4-Dimethoxyphenyl isothiocyanate 38985-64-7,  
2-Fluorophenyl isothiocyanate 40532-06-7, 2,5-Dimethoxyphenyl  
isothiocyanate 51333-75-6, 2-Methylthiophenyl isothiocyanate  
104968-58-3, 3,5-Dimethoxyphenyl isothiocyanate 139768-71-1  
190774-56-2 206761-68-4  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(preparation of aminothiadiazoles as antiproliferatives)

IT 528855-68-7P 528855-69-8P 528855-70-1P 528855-71-2P 528855-72-3P  
528855-73-4P 528855-74-5P 528855-75-6P 528855-76-7P 528855-77-8P  
528855-78-9P 528855-79-0P 528855-80-3P 528855-81-4P 528855-82-5P  
528855-83-6P 528855-84-7P 528855-85-8P 528855-86-9P 528855-87-0P  
528855-88-1P 528855-89-2P 528855-90-5P 528855-91-6P 528855-92-7P  
528855-93-8P 528855-94-9P 528855-95-0P 528855-96-1P 528855-97-2P  
528855-98-3P 528855-99-4P 528856-00-0P 528856-01-1P 528856-02-2P  
528856-03-3P 528856-04-4P 528856-05-5P 528856-06-6P 528856-07-7P  
528856-08-8P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(preparation of aminothiadiazoles as antiproliferatives)

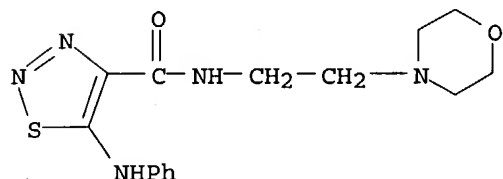
IT **528855-40-5P**  
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of aminothiadiazaoles as antiproliferatives)

RN 528855-40-5 HCAPLUS

CN 1,2,3-Thiadiazole-4-carboxamide, N-[2-(4-morpholinyl)ethyl]-5-(phenylamino)- (9CI) (CA INDEX NAME)



L108 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:676007 HCAPLUS

DN 137:216945

ED Entered STN: 08 Sep 2002

TI Preparation of substituted 2-(1H-indazol-6-ylamino)nicotinamides for treating KDR-related diseases

IN Chen, Guoqing; Adams, Jeffrey; Bemis, Jean; Croghan, Michael; Dipietro, Lucian; Dominguez, Celia; Elbaum, Daniel; Germain, Julie; Huang, Qi; Kim, Joseph L.; Ouyang, Xiaohu; Patel, Vinod F.; Smith, Leon M.; Tasker, Andrew; Xi, Ning; Xu, Shimin; Yuan, Chester Chenguang; Kim, Tae-Seong

PA Amgen Inc., USA

SO PCT Int. Appl., 395 pp.

CODEN: PIXXD2

DT Patent

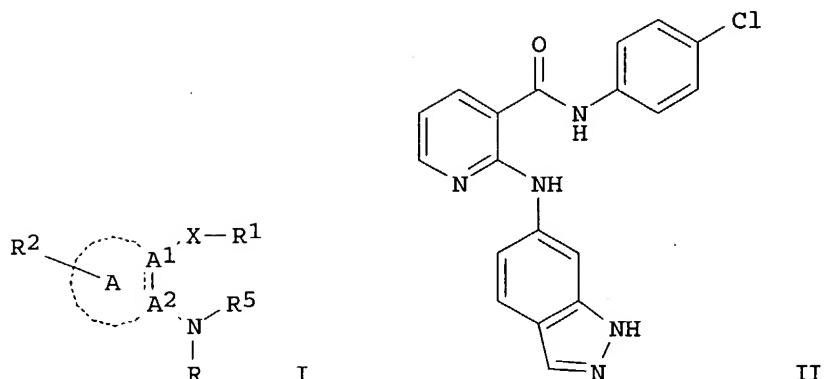
LA English

IC ICM C07D401-00

CC 28-8 (Heterocyclic Compounds (More Than One Hetero Atom))  
Section cross-reference(s): 1

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002068406	A2	20020906	WO 2002-US3064	20020111 <--
	WO 2002068406	A3	20030424		
	W:				
	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW:				
	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2003195230	A1	20031016	US 2002-46622	20020110 <--
	EE 200300325	A	20031215	EE 2003-325	20020111 <--
PRAI	US 2001-261882P	P	20010112	<--	
	US 2001-323808P	P	20010919	<--	
	US 2002-46622	A	20020110		
	WO 2002-US3064	W	20020111	<--	
OS	MARPAT 137:216945				
GI					



- AB The title compds. [I; each of A1 and A2 = C, CH, N; A = 5-6 membered partially saturated heterocyclcyl, 5-6 membered heteroaryl, 9-11 membered fused partially saturated heterocyclcyl, etc.; X = C(:Z)N(R5a)R4; Z = O, S; R = (un)substituted 4-6 membered heterocyclcyl, aryl, fused 9-14 membered bicyclic or tricyclic heterocyclcyl; R1 = (un)substituted 6-10 membered aryl, 4-6 membered heterocyclcyl, cycloalkyl, etc.; R2 = H, halo, cycloalkyl, etc.; R4 = a bond, alkylene, alkenylene, etc.; R5 = H, alkyl, (un)substituted Ph, aralkyl; R5a is not defined] which are effective for prophylaxis and treatment of diseases, such as **angiogenesis** mediated diseases, were prepared Thus, heating N-(4-chlorophenyl)-2-chloro-3-pyridinecarboxamide with 6-aminoindazole at 150° for 2 h afforded II which inhibited VEGF-stimulated HUVEC proliferation at level below 50 nM. Compds. I showed inhibition of KDR at doses less than 50  $\mu$ M.
- ST indazolylaminonicotinamide prepn KDR **angiogenesis** inhibitor antitumor; nicotinamide indazolylamino prepn KDR **angiogenesis** inhibitor antitumor; vascular endothelial growth factor receptor VEGFR2 KDR indazolylaminonicotinamide prepn
- IT Cell proliferation  
(inhibitors; preparation of substituted 2-(1H-indazol-6-ylamino)nicotinamides for treating KDR-related diseases)
- IT **Angiogenesis**  
(preparation of substituted 2-(1H-indazol-6-ylamino)nicotinamides as **angiogenesis** inhibitors)
- IT Anti-inflammatory agents  
Antitumor agents  
Human  
Inflammation  
(preparation of substituted 2-(1H-indazol-6-ylamino)nicotinamides for treating KDR-related diseases)
- IT Neoplasm  
(treatment of; preparation of substituted 2-(1H-indazol-6-ylamino)nicotinamides for treating KDR-related diseases)
- IT Vascular endothelial growth factor receptors  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(type VEGFR-2; preparation of substituted 2-(1H-indazol-6-ylamino)nicotinamides for treating KDR-related diseases)
- IT 454480-74-1P 454481-03-9P 454481-08-4P  
454481-54-0P 454481-80-2P 454481-82-4P  
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(preparation of substituted 2-(1H-indazol-6-ylamino)nicotinamides for treating KDR-related diseases)
- IT 453564-50-6P 454480-67-2P 454480-68-3P

454480-69-4P 454480-70-7P 454480-71-8P  
 454480-72-9P 454480-73-0P 454480-75-2P  
 454480-76-3P 454480-77-4P 454480-78-5P  
 454480-79-6P 454480-80-9P 454480-81-0P  
 454480-82-1P 454480-83-2P 454480-84-3P  
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 454482-01-0P 454482-02-1P 454482-03-2P  
 454482-04-3P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
 (Uses)

(preparation of substituted 2-(1H-indazol-6-ylamino)nicotinamides for  
 treating KDR-related diseases)

IT 67-64-1, Acetone, reactions 106-47-8, 4-Chloroaniline, reactions  
 106-52-5, 4-Hydroxy-1-methylpiperidine 110-91-8, Morpholine, reactions  
 111-77-3, 2-(2-Methoxyethoxy)ethan-1-ol 123-00-2, 4-(3-  
 Aminopropyl)morpholine 139-59-3, 4-Phenoxyaniline 372-48-5,  
 2-Fluoropyridine 580-15-4, 6-Aminoquinoline 722-92-9,  
 [4-[2,2,2-Trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]amine  
 1083-48-3, 4-(4-Nitrobenzyl)pyridine 1202-00-2, [2-(2-  
 Aminophenoxy)ethyl]dimethylamine 1445-73-4, 1-Methylpiperidin-4-one  
 1458-98-6, 3-Bromo-2-methylpropene 1692-15-5, 4-Pyridylboronic acid  
 2008-75-5, 1-(2-Chloroethyl)piperidine hydrochloride 2393-23-9,  
 p-Methoxybenzylamine 2942-59-8, 2-Chloronicotinic acid 3282-56-2,  
 1-tert-Butyl-4-nitrobenzene 3554-65-2, (1-Methylpyrrolidin-2-yl)methanol  
 4535-90-4 6146-52-7, 5-Nitroindole 6310-21-0, 2-tert-Butylaniline  
 6967-12-0, 6-Aminoindazole 7223-38-3, 1-(Dimethylamino)-2-propyne  
 10403-47-1, 2-Bromo-5-nitroaniline 19727-83-4, 6-Nitroindoline

33252-30-1, 2-Chloro-4-cyanopyridine 49609-84-9, 2-Chloronicotinoyl chloride 53062-99-0 54962-75-3, 3-Bromo-5-trifluoromethylaniline 56149-31-6 57841-51-7 58021-55-9 59115-08-1, 2-Methyl-2-(4-nitrophenyl)propionic acid methyl ester 74728-65-7, 1-Methyl-6-amino-1H-indazole 79099-07-3, N-tert-Butoxycarbonylpiperidin-4-one 80887-01-0, 2-Bromo-5-nitrobenzoyl chloride 114262-65-6, (4-(1,1,2,2,3,3,4,4,4-Nonafluorobutyl)phenyl)amine 117242-06-5, 4,4-Dimethyl-7-nitro-3,4-dihydro-2H-isoquinolin-1-one 132873-57-5 137076-22-3, N-tert-Butoxycarbonyl-4-formylpiperidine 148546-99-0, 1-(5-Aminophenyl)-4-methylpiperazine 173094-82-1, 2-(1H-Indazol-6-ylamino)pyridine-3-carboxylic acid 442847-11-2, 2-tert-Butyl-5-nitrophenol 453560-86-6, (4-Boc-piperazin-1-yl)(3-nitro-5-trifluoromethylphenyl)methanone 453560-89-9, [3-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-5-trifluoromethylphenyl]amine 453562-51-1, [2-[4-(tert-Butyl)-2-aminophenoxy]ethyl]dimethylamine 453562-53-3, 1-[2-tert-Butyl-5-aminophenyl]-4-methylpiperazine 453562-79-3, [4-(1,1-Dimethyl-3-(morpholin-4-yl)propyl)phenyl]amine 453562-90-8, 4-(Tert-Butyl)-3-(3-piperidylpropyl)phenylamine 453562-95-3, (1-(2-(Morpholin-4-yl)ethyl)indol-6-yl)amine 453563-09-2  
**454481-81-3** 454482-09-8, 4-(tert-Butyl)-2-(4-methylpiperazinyl)phenylamine 454482-10-1 454482-11-2 454482-12-3, 4-(1-Methyl-4-piperidinyl)phenylamine 454482-13-4, 3-(3-Aminophenyl)-1-(4-methylpiperazinyl)propan-1-one 454482-14-5 454482-15-6, [1-(2-Pyridyl)pyrrolidin-3-yl]amine 454482-16-7 454482-17-8  
 RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of substituted 2-(1H-indazol-6-ylamino)nicotinamides for treating KDR-related diseases)

IT 393-55-5P, 2-Fluoronicotinic acid 6310-17-4P, 2-Bromo-1-tert-butyl-4-nitrobenzene 20691-89-8P, (1-Methylpiperidin-4-yl)methanol 54815-23-5P, 2-(4-Aminophenyl)-2-methylpropionic acid methyl ester 90221-50-4P 105807-84-9P, 6-Amino-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one 106516-27-2P 144293-82-3P, 1-(2,2-Dimethyl-6-nitro-2,3-dihydrobenzo[1,4]oxazin-4-yl)ethanone 144293-83-4P, 1-(6-Amino-2,2-dimethyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)ethanone 177947-88-5P 179898-72-7P, 3,3-Dimethyl-6-nitroindoline 180692-27-7P 182564-38-1P 255060-77-6P 442846-54-0P 442846-55-1P 442846-56-2P 442846-58-4P 442846-59-5P 442846-60-8P 442846-61-9P, 7-Amino-2-(4-methoxybenzyl)-4,4-dimethyl-3,4-dihydro-2H-isoquinolin-1-one 442846-62-0P 442846-63-1P, 1-(7-Amino-4,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)ethanone 442846-64-2P 442846-65-3P 442846-67-5P 442846-68-6P 442846-69-7P 442846-70-0P 442846-71-1P 442846-72-2P 442846-73-3P 442846-74-4P 442846-75-5P 442846-76-6P 442846-77-7P 442846-78-8P 442846-79-9P 442846-80-2P 442846-81-3P 442846-82-4P 442846-83-5P 442846-84-6P 442846-85-7P 442846-86-8P 442846-87-9P 442846-88-0P, 1-[2-(2-tert-Butyl-5-nitrophenoxy)ethyl]piperidine 442846-89-1P, 3,3-Dimethyl-1-(1-methylpiperidin-4-yl)-6-nitro-2,3-dihydro-1H-indole 442846-90-4P 442846-91-5P, 1-(4,4-Dimethyl-7-nitro-3,4-dihydro-1H-isoquinolin-2-yl)ethanone 442846-92-6P, 2-Bromo-N-(4-methoxybenzyl)-5-nitrobenzamide 442846-93-7P, 4,4-Dimethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline 442846-94-8P, 1-Boc-4-(3-nitro-5-trifluoromethylbenzyl)piperazine 442846-98-2P, 1-Methyl-4-(4-nitrobenzyl)-1,2,3,6-tetrahydro-pyridine 442847-02-1P 442847-03-2P 442847-04-3P 442847-06-5P, 4-(2-tert-Butyl-5-nitrophenyl)pyridine 442847-07-6P 442847-08-7P, 4-tert-Butyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)aniline 452929-03-2P, 1-[2-tert-Butylphenyl]-4-methylpiperazine 453560-51-5P 453560-61-7P 453560-62-8P 453560-87-7P 453560-88-8P 453562-54-4P, 1-[2-tert-Butyl-5-nitrophenyl]-4-methylpiperazine 453562-59-9P 453562-60-2P 453562-67-9P 453562-68-0P, 1-(3,3-Dimethyl-6-nitro-2,3-dihydro-indol-1-yl)ethanone 454482-05-4P, 2-(6-Quinolylamino)pyridine-3-carboxylic acid 454482-06-5P 454482-07-6P **454482-08-7P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of substituted 2-(1H-indazol-6-ylamino)nicotinamides for treating KDR-related diseases)

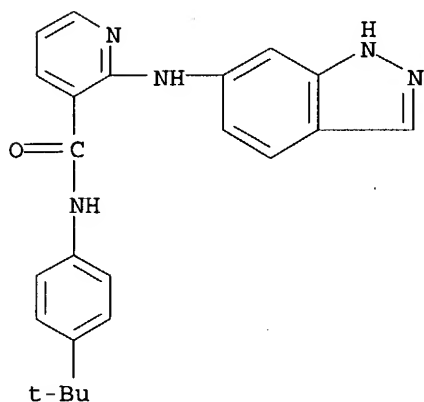
IT 454480-74-1P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of substituted 2-(1H-indazol-6-ylamino)nicotinamides for treating KDR-related diseases)

RN 454480-74-1 HCAPLUS

CN 3-Pyridinecarboxamide, N-[4-(1,1-dimethylethyl)phenyl]-2-(1H-indazol-6-ylamino)- (9CI) (CA INDEX NAME)



L108 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:658116 HCAPLUS

DN 137:201332

ED Entered STN: 30 Aug 2002

TI Preparation of heterocyclylalkylamine derivatives as remedies for angiogenesis mediated diseases

IN Chen, Guoqing; Adams, Jeffrey; Bemis, Jean; Booker, Shon; Cai, Guolin; Croghan, Michael; Dipietro, Lucian; Dominguez, Celia; Elbaum, Daniel; Germain, Julie; Geuns-meyer, Stephanie; Handley, Michael; Huang, Qi; Kim, Joseph L.; Kim, Tae-seong; Kiselyov, Alexander; Ouyang, Xiaohu; Patel, Vinod F.; Smith, Leon M.; Stec, Markian; Tasker, Andrew; Xi, Ning; Xu, Shimin; Yuan, Chester Chenguang

PA Amgen Inc., USA

SO PCT Int. Appl., 502 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07D409-12

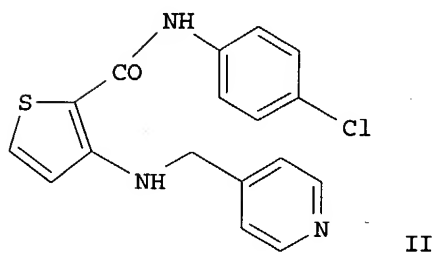
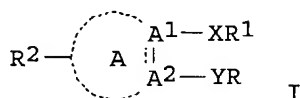
ICS C07D409-14; C07D213-82; C07D401-12; C07D401-14; C07D409-04; C07D413-14; C07D417-14; C07D405-14; C07D405-12

CC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))  
Section cross-reference(s): 1, 63

FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002066470	A1	20020829	WO 2002-US743	20020111 <--
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 CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,  
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 US 2001-323764P P 20010919  
 US 2002-46681 A 20020110  
 WO 2002-US743 W 20020111  
 OS MARPAT 137:201332  
 GI



AB Title compds. [I; A1, A2 independently = C, N; A = 5-, or 6-membered partially saturated heterocyclyl, 5-, or 6-membered heterocyclyl, 9-, or 10-membered fused partially saturated heterocyclyl, 9-, 10-, or 11-membered fused heteroaryl, naphthyl, 4-, 5-, or 6-membered cycloalkenyl; X = C:ZNR3, C:ZN(R3)R4; Z = O, S; Y = N:CH, NR5(CR6R7), R8N(R5)(CR6R7), NR5(CR6R7)R8; R = 5-, or 6-membered (un)substituted heterocyclyl, 9-, 10-, 11-membered heterocyclyl; R1 = 6-10-membered (un)substituted aryl, 5-, or 6-membered (un)substituted heterocyclyl, 9-11 membered (un)substituted fused heterocyclyl, cycloalkyl, cycloalkenyl; R2 = H, halo, oxo, SH, COOH, CHO; R3 = H, alkyl, 5-, or 6-membered heterocyclyl; R4 = alkylenyl, alkenylenyl, alkynylenyl; R5 = H, alkyl, aralkyl, C6H5; R6, R7 independently = H, halo, CN, alkyl; R6R7 = cycloalkyl; R8 = alkylenyl; etc.] are prepared and are effective for prophylaxis and treatment of diseases, such as **angiogenesis** mediated diseases. The invention encompasses novel compds., analogs, prodrugs and pharmaceutically acceptable derivs. thereof, pharmaceutical compns. and methods for prophylaxis and treatment of diseases and other maladies or conditions involving, cancer and the like. The subject invention also relates to processes for making such compds. as well as to intermediates useful in such processes. Thus, the title compound II was prepared from Me 3-amino-2-thiophenecarboxylate, 4-chloroaniline, and 4-pyridine carboxaldehyde via coupling reaction.

ST heterocyclylalkylamine prepn remedy **angiogenesis** mediation

disease

IT **Angiogenesis**  
 Antitumor agents  
 Cell proliferation  
 Human  
 Inflammation  
 Neoplasm  
 (preparation of heterocyclylalkylamine derivs. as remedies for **angiogenesis** mediated diseases)

IT Coupling reaction  
 (process for preparing heterocyclylalkylamine derivs. as remedies for **angiogenesis** mediated diseases)

IT Drug delivery systems  
 (prodrugs; preparation of heterocyclylalkylamine derivs. as remedies for **angiogenesis** mediated diseases)

IT 453561-03-0P 453561-73-4P 453561-77-8P 453561-95-0P 453562-83-9P  
 453563-07-0P 453563-37-6P 453563-79-6P 453564-01-7P  
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (preparation of heterocyclylalkylamine derivs. as remedies for **angiogenesis** mediated diseases)

IT 352227-57-7P, 2-[(Pyridin-4-ylmethyl)amino]-N-(3-trifluoromethylphenyl)nicotinamide 352227-65-7P 352227-72-6P  
 352227-74-8P 453560-98-0P 453561-00-7P 453561-01-8P 453561-02-9P  
 453561-04-1P 453561-05-2P 453561-06-3P 453561-07-4P 453561-08-5P  
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 453561-72-3P 453561-75-6P 453561-76-7P 453561-78-9P 453561-80-3P  
 453561-81-4P, 2-[(2,3-Dihydrobenzofuran-5-ylmethyl)amino]-N-[3,3-dimethyl-1-(piperidin-4-ylmethyl)-2,3-dihydro-1H-indol-6-yl]nicotinamide  
 453561-82-5P 453561-83-6P 453561-84-7P 453561-85-8P,  
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RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of heterocyclylalkylamine derivs. as remedies for angiogenesis mediated diseases)

IT	453563-88-7P	453563-89-8P	453563-90-1P	453563-91-2P	453563-92-3P
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	453565-10-1P	453565-11-2P	453565-12-3P	453565-13-4P	453565-14-5P
	453565-15-6P	453565-16-7P	453565-17-8P	453565-18-9P	453565-19-0P
	453565-20-3P	453565-21-4P	453565-22-5P	453565-23-6P	453565-24-7P
	453565-25-8P	453565-26-9P	453565-27-0P	453565-28-1P	453565-29-2P
	453565-30-5P	453565-31-6P	453565-32-7P	453565-33-8P	

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of heterocyclylalkylamine derivs. as remedies for

**angiogenesis mediated diseases)**

- IT 55-86-7 79-04-9, Chloroacetyl chloride 98-16-8, 3-(Trifluoromethyl)aniline 99-09-2, 3-Nitroaniline 99-57-0, 2-Amino-4-nitrophenol 99-88-7, 4-Isopropylaniline 106-47-8, 4-Chloroaniline, reactions 106-52-5, 4-Hydroxy-1-methylpiperidine 108-01-0, N,N-Dimethylethanolamine 108-23-6, Isopropyl chloroformate 109-01-3, N-Methylpiperazine 109-72-8, Butyllithium, reactions 110-89-4, Piperidine, reactions 121-51-7, 3-Nitrobenzenesulfonyl chloride 123-00-2, 4-Morpholinepropanamine 139-59-3, 4-Phenoxyaniline 288-88-0, 1H-1,2,4-Triazole 328-79-0, 1-Methoxy-3-nitro-5-trifluoromethylbenzene 328-80-3 350-46-9, 1-Fluoro-4-nitrobenzene 372-48-5, 2-Fluoropyridine 527-72-0, 2-Thienylcarboxylic acid 541-41-3, Ethyl chloroformate 609-71-2, 2-Hydroxynicotinic acid 628-13-7, Pyridine hydrochloride 722-92-9, 2-(4-Aminophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol 769-92-6, 4-tert-Butylaniline 872-85-5, 4-Pyridinecarboxaldehyde 1083-48-3, 4-(4-Nitrobenzyl)pyridine 1118-68-9, Dimethylaminoacetic acid 1126-09-6, Piperidine-4-carboxylic acid ethyl ester 1445-73-4, N-Methyl-4-piperidone 1458-98-6, 3-Bromo-2-methylpropene 1692-15-5, 4-Pyridylboronic acid 1704-62-7, 2-[2-(Dimethylamino)ethoxy]ethanol 2008-75-5, 1-(2-Chloroethyl)piperidine hydrochloride 2221-00-3, (4-Imidazolylphenyl)amine 2435-50-9, Pyrimidine-4-carboxaldehyde 2942-59-8, 2-Chloronicotinic acid 3040-44-6, 2-(Piperid-1-yl)ethanol 3279-07-0, 2-Nitro-4-tert-butylphenol 3282-56-2, 4-tert-Butylnitrobenzene 3438-46-8, 4-Methylpyrimidine 3554-65-2 3647-69-6, 4-(2-Chloroethyl)morpholine hydrochloride 3731-53-1, 4-Aminomethylpyridine 4009-98-7, Methoxymethyltriphenylphosphonium chloride 4160-54-7, 1,3-Dinitro-4-tert-butylbenzene 4769-96-4, 6-Nitroindole 5345-47-1, 2-Aminonicotinic acid 5458-84-4, 2-Iodo-5-nitroanisole 5909-24-0, Ethyl 4-chloro-2-methylthiopyrimidine-5-carboxylate 6146-52-7, 5-Nitroindole 6165-69-1, 3-Thiopheneboronic acid 6310-21-0, 2-tert-Butylaniline 6457-49-4, 4-Piperidylmethanol 7223-38-3, 1-Dimethylamino-2-propyne 10403-47-1, 2-Bromo-5-nitroaniline 13258-63-4, 4-(2-Aminoethyl)pyridine 14446-67-4, 1-Allylpiperidine 19727-83-4, 6-Nitroindoline 19910-33-9, 2-(4-Nitrophenyl)propionic acid 20769-85-1, 2-Bromo-2-methylpropionyl bromide 22288-78-4, Methyl 3-amino-2-thiophenecarboxylate 24424-99-5, Di-tert-butyl dicarbonate 24954-67-4, 2-(4-Nitrophenyl)ethylamine 30529-70-5, 2-Chloro-6-methylnicotinic acid 33252-30-1, 2-Chloro-4-cyanopyridine 54962-75-3, 3-Bromo-5-(trifluoromethyl)phenylamine 57260-71-6, N-Boc-piperazine 60979-14-8, 1-Nitro-4-(1,1,2,2,2-pentafluoroethyl)benzene 71999-74-1 74764-17-3, 2-(2-Pyridylamino)ethylamine 75833-38-4, 2-Chloropyrimidine-4-carbonitrile 80887-01-0, 2-Bromo-5-nitrobenzoyl chloride 102362-98-1, 3,3-Dimethyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide 105612-50-8 109384-19-2, 1-Boc-4-hydroxypiperidine 110073-17-1, Methyl 2-(morpholin-4-yl)propionate 119899-26-2, 2-Fluoropyridine-3-carbonyl chloride 148546-99-0, 3-(4-Methylpiperazinyl)phenylamine 171178-50-0, 2,6-Difluoropyridine-3-carboxylic acid 183946-06-7, 2-Methyl-4-nitro-1-pentafluoroethylbenzene 201733-56-4 453560-55-9, 1-Boc-2-(3-nitro-5-trifluoromethylphenoxy)methylpyrrolidine 453560-61-7, 3,3-Dimethyl-1-(1-Boc-piperidin-4-ylmethyl)-6-nitro-2,3-dihydro-1H-indole 453560-62-8 453560-64-0, 2-Methoxy-4-nitro-1-pentafluoroethylbenzene 453560-68-4 453560-72-0, (S)-2-Chloro-N-[4-(2-oxiranylmethoxy)-3-pentafluoroethylphenyl]nicotinamide 453560-93-5, 1-Methyl-4-[1-methyl-1-(4-nitrophenyl)ethyl]pyridinium 453561-19-8 453561-74-5 453563-30-9, 2-Fluoro-N-(4-trifluoromethylphenyl)nicotinamide 453563-31-0, [[2-(1-Isopropylazetid-3-ylmethoxy)pyridin-4-yl]methyl]amine 453564-35-7, 2-Amino-N-(4-pentafluoroethylphenyl)nicotinamide
- RL: RCT (Reactant); RACT (Reactant or reagent)
- (preparation of heterocyclalkylamine derivs. as remedies for **angiogenesis mediated diseases)**
- IT 349-57-5P, 3-Nitro-5-trifluoromethylphenol 393-55-5P, 2-Fluoronicotinic

acid 6310-17-4P, 2-Bromo-1-tert-butyl-4-nitrobenzene 6425-46-3P,  
4-[(4-Nitrophenyl)methyl]morpholine 13669-28-8P, 1-Methyl-4-  
methylenepiperidine 16153-81-4P, 4-Methyl-1-(4-aminophenyl)piperazine  
16155-03-6P, 4-Methyl-1-(4-nitrophenyl)piperazine 18755-53-8P,  
2-Methyl-2-(4-nitrophenyl)propan-1-ol 20691-89-8P, (1-Methylpiperidin-4-  
yl)methanol 24252-37-7P, 1-Methylpiperidine-4-carboxylic acid ethyl  
ester 29241-65-4P, 5-Bromo-2-chloronicotinic acid 31951-12-9P  
51013-67-3P, 4-(Morpholin-4-ylmethyl)phenylamine 51444-31-6P,  
2-(1,2,4-Triazolyl)ethylamine 53062-99-0P 54815-23-5P,  
2-(4-Aminophenyl)-2-methylpropionic acid methyl ester 56329-05-6P  
57841-51-7P 59115-08-1P, 2-Methyl-2-(4-nitrophenyl)propionic acid methyl  
ester 60979-04-6P, 4-(1,1,2,2,2-Pentafluoroethyl)phenylamine  
69296-06-6P, 2-Morpholin-4-ylpropanol 72716-86-0P, 4-Cyano-2-  
methoxypyridine 85160-84-5P, 2,2-Dimethyl-6-nitro-4H-benzo[1,4]oxazin-3-  
one 90221-50-4P, N-(2-Bromo-5-nitrophenyl)acetamide 91133-58-3P  
94838-59-2P 100973-67-9P 101537-64-8P, 3-[(tert-  
Butoxy)carbonylamino]thiophene-2-carboxylic acid 103392-84-3P,  
2-tert-Butyl-5-nitroaniline 104612-36-4P, 5-Bromo-2-hydroxynicotinic  
acid 105807-77-0P, 2,2,4-Trimethyl-6-nitro-4H-benzo[1,4]oxazin-3-one  
105807-84-9P, 6-Amino-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one  
106516-27-2P, 3-(1-Methyl-1,2,3,6-tetrahydropyridin-4-yl)-5-nitro-1H-  
indole 117242-06-5P, 4,4-Dimethyl-7-nitro-3,4-dihydro-2H-isoquinolin-1-  
one 136545-11-4P, 2,2-Dimethyl-6-nitro-3,4-dihydro-2H-benzo[1,4]oxazine  
137076-22-3P, 1-Boc-4-formylpiperidine 140837-70-3P,  
3,3-Dimethyl-6-nitro-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide  
142253-56-3P, 1-Boc-3-Hydroxymethylazetidine 142253-57-4P,  
Methanesulfonic acid N-Boc-azetidin-3-ylmethyl ester 142851-03-4P,  
1-Boc-piperidine-4-carboxylic acid ethyl ester 143094-45-5P,  
5-Bromo-2-chloro-N-(4-chlorophenyl)nicotinamide 144226-16-4P  
144293-82-3P, 1-(2,2-Dimethyl-6-nitro-2,3-dihydrobenzo[1,4]oxazin-4-  
yl)ethanone 144293-83-4P, 1-(6-Amino-2,2-dimethyl-2,3-  
dihydrobenzo[1,4]oxazin-4-yl)ethanone 148900-69-0P, ((2-Methoxy-4-  
pyridyl)methyl)amine 149532-90-1P, ((2-Methoxypyridin-4-yl)methyl)amine  
hydrochloride 161975-39-9P, 1-Boc-4-methylsulfonyloxymethylpiperidine  
179898-72-7P, 3,3-Dimethyl-6-nitroindoline 180692-27-7P,  
Trifluoromethanesulfonic acid 1-methyl-1,2,3,6-tetrahydropyridin-4-yl  
ester 181363-19-9P 182564-38-1P, 3-(1-Methyl-4-piperidyl)indole-5-  
ylamine 436095-35-1P, 3-[(4-Methylpiperazinyl)sulfonyl]phenylamine  
442846-54-0P, [(2-(1-Methylpiperidin-4-yloxy)pyridin-4-yl)methyl]amine  
442846-55-1P, [(2-(1-Methylpyrrolidin-2-ylmethoxy)pyridin-4-  
yl)methyl]amine 442846-56-2P, (4-Aminomethylpyridin-2-yl)(3-morpholin-4-  
ylpropyl)amine 442846-58-4P, [(2-(1-Methylpiperidin-4-ylmethoxy)pyridin-  
4-yl)methyl]amine 442846-59-5P, 3-(4-Boc-piperazin-1-ylmethyl)-5-  
trifluoromethylphenylamine 442846-60-8P, (3-(4-Methylpiperazin-1-  
ylmethyl)-4-pentafluoroethylphenyl)amine 442846-61-9P,  
7-Amino-2-(4-methoxybenzyl)-4,4-dimethyl-3,4-dihydro-2H-isoquinolin-1-one  
442846-62-0P, (3-Amino-5-trifluoromethylphenyl)(4-Boc-piperazin-1-  
yl)methanone 442846-63-1P, 1-(7-Amino-4,4-dimethyl-3,4-dihydro-1H-  
isoquinolin-2-yl)ethanone 442846-64-2P, 4-tert-Butyl-3-(1-Boc-pyrrolidin-  
3-ylmethoxy)phenylamine 442846-65-3P, 4-tert-Butyl-3-(1-Boc-azetidin-3-  
ylmethoxy)phenylamine 442846-67-5P, N-(4-Acetyl-2,2-dimethyl-3,4-dihydro-  
2H-benzo[1,4]oxazin-6-yl)-2-fluoronicotinamide 442846-68-6P,  
2-Fluoro-N-(2,2,4-trimethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-  
yl)nicotinamide 442846-69-7P, N-(2,2-Dimethyl-3-oxo-3,4-dihydro-2H-  
benzo[1,4]oxazin-6-yl)-2-fluoronicotinamide 442846-70-0P,  
2-Fluoro-N-[3-(4-methylpiperazin-1-ylmethyl)-5-  
trifluoromethylphenyl]nicotinamide 442846-71-1P, 2-Fluoro-N-(2-Boc-4,4-  
dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)nicotinamide 442846-72-2P,  
2-Fluoro-N-[3-(4-methylpiperazin-1-ylmethyl)-4-  
pentafluoromethylphenyl]nicotinamide 442846-73-3P, 2-Fluoro-N-(4,4-  
dimethyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)nicotinamide  
442846-74-4P, 2-Fluoro-N-[3-((4-Boc-piperazin-1-yl)carbonyl)-5-  
trifluoromethylphenyl]nicotinamide 442846-75-5P, 2-Fluoro-N-[3-(4-Boc-

piperazin-1-ylmethyl)-5-trifluoromethylphenyl]nicotinamide 442846-76-6P,  
N-(2-Acetyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-fluoronicotinamide 442846-77-7P, N-[3,3-Dimethyl-1-(1-methylpiperidin-4-yl)-2,3-dihydro-1H-indol-6-yl]-2-fluoronicotinamide 442846-78-8P,  
2-Fluoro-N-[3-(1-Boc-azetidin-3-ylmethoxy)-5-trifluoromethylphenyl]nicotinamide 442846-79-9P, (S)-N-[4-tert-Butyl-3-(1-Boc-pyrrolidin-2-ylmethoxy)phenyl]-2-fluoronicotinamide 442846-80-2P,  
2-Chloro-N-[2-(4-methoxybenzyl)-4,4-dimethyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]nicotinamide 442846-81-3P,  
2-Chloro-N-(4,4-dimethyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)nicotinamide 442846-82-4P, 2-[3-[(2-Chloropyridine-3-carbonyl)amino]phenyl]-2-methylpropionic acid methyl ester 442846-83-5P,  
N-[4-tert-Butyl-3-[2-(1-Boc-piperidin-4-yl)ethyl]phenyl]-2-chloronicotinamide 442846-84-6P 442846-85-7P 442846-86-8P  
442846-87-9P 442846-88-0P, 1-[2-(2-tert-Butyl-5-nitrophenoxy)ethyl]piperidine 442846-90-4P 442846-91-5P,  
1-(4,4-Dimethyl-7-nitro-3,4-dihydro-1H-isoquinolin-2-yl)ethanone 442846-92-6P, 2-Bromo-N-(4-methoxybenzyl)-5-nitrobenzamide 442846-93-7P,  
4,4-Dimethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline 442846-94-8P,  
1-Boc-4-(3-nitro-5-trifluoromethylbenzyl)piperazine 442846-97-1P,  
1-Methyl-4-[1-methyl-1-(4-nitrophenyl)ethyl]pyridinium iodide 442846-98-2P, 1-Methyl-4-(4-nitrobenzyl)-1,2,3,6-tetrahydropyridine 442847-02-1P 442847-03-2P, [3-[3-Amino-5-(trifluoromethyl)phenyl]propyn-2-yl]dimethylamine 442847-04-3P, [3-[3-Amino-5-(trifluoromethyl)phenyl]propyl]dimethylamine 442847-06-5P,  
4-(2-tert-Butyl-5-nitrophenyl)pyridine 442847-07-6P 442847-08-7P,  
4-tert-Butyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)aniline 442847-11-2P, 2-tert-Butyl-5-nitrophenol 452929-03-2P,  
1-(2-tert-Butylphenyl)-4-methylpiperazine 453560-49-1P,  
1-Boc-4-(3-nitro-5-trifluoromethylphenoxy)piperidine 453560-50-4P,  
1-Boc-4-(3-amino-5-trifluoromethylphenoxy)piperidine 453560-51-5P,  
(S)-4-tert-Butyl-3-(1-Boc-pyrrolidin-2-ylmethoxy)phenylamine 453560-52-6P 453560-53-7P, N-[3-(1-Methylpiperidin-4-yl)-5-trifluoromethylphenyl]-2-fluoronicotinamide 453560-54-8P,  
2-(3-Nitro-5-trifluoromethylphenoxy)methylpyrrolidine 453560-56-0P,  
1-Methyl-2-(3-nitro-5-trifluoromethylphenoxy)methylpyrrolidine 453560-57-1P, N-(3-Bromo-5-trifluoromethylphenyl)acetamide 453560-58-2P  
453560-59-3P 453560-60-6P, 3,3-Dimethyl-6-nitro-1-(piperidin-4-ylmethyl)-2,3-dihydro-1H-indole 453560-63-9P, 5-Nitro-2-pentafluoroethylphenol 453560-66-2P 453560-67-3P 453560-69-5P 453560-70-8P 453560-71-9P,  
(S)-2-Chloro-N-[4-(2-hydroxy-3-(pyrrolidin-1-yl)propoxy)-3-pentafluoroethylphenyl]nicotinamide 453560-73-1P 453560-74-2P,  
5-Nitro-2-trifluoromethylanisole 453560-76-4P 453560-77-5P,  
(R)-2-Chloro-N-[3-(2-hydroxy-2-(pyrrolidin-1-yl)propoxy)-4-pentafluoroethylphenyl]nicotinamide 453560-78-6P, 2-Dimethylamino-1-(3,3-dimethyl-6-nitro-2,3-dihydroindol-1-yl)ethanone 453560-79-7P  
453560-80-0P, 2-Boc-4,4-dimethyl-7-nitro-1,2,3,4-tetrahydroisoquinoline 453560-81-1P 453560-82-2P, 2-(4-Methoxybenzyl)-4,4-dimethyl-7-nitro-3,4-dihydro-2H-isoquinolin-1-one 453560-83-3P, 2-Bromomethyl-4-nitro-1-pentafluoroethylbenzene 453560-84-4P 453560-85-5P 453560-86-6P,  
(4-Boc-piperazin-1-yl)(3-nitro-5-trifluoromethylphenyl)methanone 453560-87-7P 453560-88-8P 453560-89-9P, 3-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-5-trifluoromethylphenylamine 453560-90-2P,  
1-Boc-3-(3-nitro-5-trifluoromethylphenoxy)methylazetidine 453560-91-3P,  
2-Bromo-N-(2-hydroxy-5-nitrophenyl)-2-methylpropionamide 453560-92-4P,  
4-[1-(2-Bromo-4-nitrophenyl)-1-methylethyl]-1-methylpyridinium iodide 453560-94-6P, 4-[1-(2-Bromo-4-nitrophenyl)-1-methylethyl]-1-methyl-1,2,3,6-tetrahydropyridine 453560-95-7P, 4-(2-tert-Butyl-5-nitrophenyl)but-3-en-1-ol 453560-96-8P, 4-(2-tert-Butyl-5-nitrophenyl)but-3-enal 453560-97-9P, 1-[4-(2-tert-Butyl-5-nitrophenyl)but-3-enyl]pyrrolidine 453560-99-1P 453561-10-9P, 6-Methyl-2-[(4-pyridylmethyl)amino]pyridine-3-carboxylic acid 453561-25-6P, 5-(3-Thiophene)-2-chloro-N-(4-chlorophenyl)nicotinamide 453561-30-3P 453561-31-4P 453562-01-1P,

3-[(4-Methylpiperazinyl)sulfonyl]-1-nitrobenzene 453562-06-6P  
 453562-50-0P, [2-[4-(tert-Butyl)-2-nitrophenoxy]ethyl]dimethylamine  
 453562-51-1P, [2-[4-(tert-Butyl)-2-aminophenoxy]ethyl]dimethylamine  
 453562-53-3P, 1-[2-(tert-Butyl)-5-aminophenyl]-4-methylpiperazine  
 453562-54-4P, 1-[2-(tert-Butyl)-5-nitrophenyl]-4-methylpiperazine  
 453562-59-9P 453562-60-2P, 1-(1-Methyl-4-piperidyl)indoline-6-ylamine  
 453562-63-5P, 1-(6-Nitroindolinyl)-2-piperidylethan-1-one 453562-64-6P,  
 1-(2-Piperidylethyl)indoline-6-ylamine 453562-67-9P,  
 N-(2-Bromo-5-nitrophenyl)-N-(2-methylprop-2-enyl)acetamide 453562-68-0P  
 453562-71-5P, 1-Acetyl-6-amino-3,3-dimethylindoline 453562-74-8P  
 453562-77-1P, 2-Methyl-2-(4-nitrophenyl)propionaldehyde 453562-78-2P,  
 4-[3-Methyl-3-(4-nitrophenyl)butyl]morpholine 453562-79-3P,  
 4-(1,1-Dimethyl-3-(morpholin-4-yl)propyl)phenylamine 453562-88-4P,  
 (2E)-3-[2-(tert-Butyl)-5-nitrophenyl]-1-(piperid-1-yl)prop-2-en-1-one  
 453562-89-5P, (2E)-3-[2-(tert-Butyl)-5-aminophenyl]-1-(piperid-1-yl)prop-2-  
 en-1-one 453562-90-8P, 4-(tert-Butyl)-3-(3-piperidylpropyl)phenylamine  
 453562-95-3P, (1-(2-(Morpholin-4-yl)ethyl)indole-6-yl)amine 453563-01-4P  
 453563-03-6P, 2-[2-[2-(Dimethylamino)ethoxy]ethoxy]pyridine-4-carbonitrile  
 453563-04-7P 453563-05-8P, N-[4-(tert-Butyl)phenyl]-2-fluoropyridine-3-  
 carboxamide 453563-09-2P, N-(4-tert-Butylphenyl)-2,6-  
 difluoronicotinamide 453563-19-4P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)

(preparation of heterocyclalkylamine derivs. as remedies for  
 angiogenesis mediated diseases)

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD

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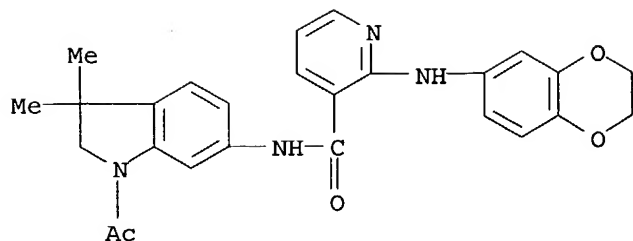
IT 453564-16-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
 (Uses)

(preparation of heterocyclalkylamine derivs. as remedies for  
 angiogenesis mediated diseases)

RN 453564-16-4 HCAPLUS

CN 3-Pyridinecarboxamide, N-(1-acetyl-2,3-dihydro-3,3-dimethyl-1H-indol-6-yl)-  
 2-[(2,3-dihydro-1,4-benzodioxin-6-yl)amino]- (9CI) (CA INDEX NAME)



L108 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:555470 HCAPLUS

DN 137:125160

ED Entered STN: 26 Jul 2002

TI Preparation of 1,2,4-triazole-3,5-diamine derivatives as kinase inhibitors

IN Lin, Ronghui; Connolly, Peter J.; Wetter, Steven; Huang, Shenlin; Emanuel, Stuart; Guninger, Robert; Middleton, Steve

PA Ortho McNeil Pharmaceutical, Inc., USA

SO PCT Int. Appl., 147 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07D249-14

ICS C07D409-06; C07D405-06; C07D401-06; C07D413-06; C07D417-06;

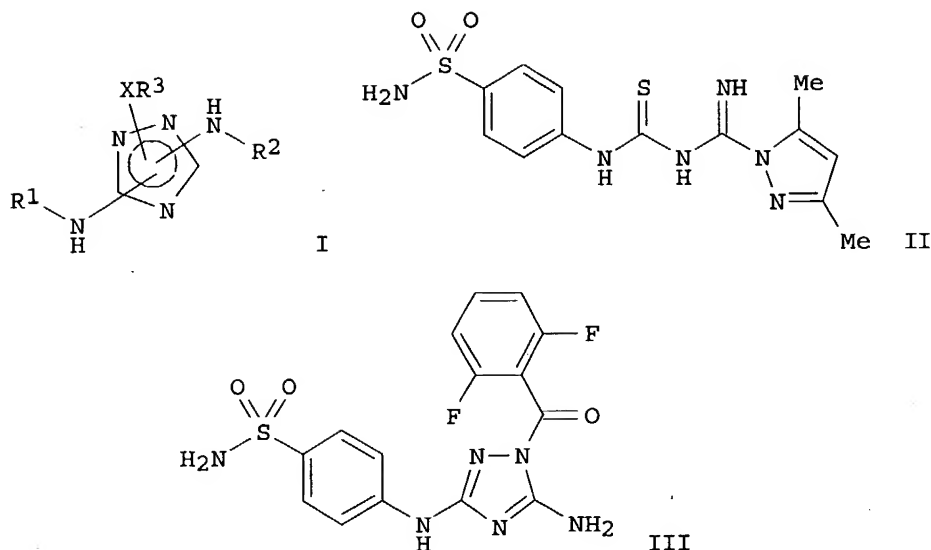
C07D403-12; C07D417-14; C07D409-14; A61K031-4196; A61K031-4439

CC 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002057240	A1	20020725	WO 2001-US50559	20011221 <--
W:			AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM	
RW:			GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG	
EP 1355889	A1	20031029	EP 2001-998116	20011221 <--
R:			AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR	
BR 2001016792	A	20040217	BR 2001-16792	20011221 <--
US 2004077699	A1	20040422	US 2001-29750	20011221 <--
NO 2003002848	A	20030820	NO 2003-2848	20030620 <--
PRAI US 2000-257703P	P	20001222 <--		
WO 2001-US50559	W	20011221		
OS MARPAT 137:125160				
GI				



AB The title derivs. [I; R1 = (un)substituted C1-8 alkyl, cycloalkyl, heterocyclyl, (hetero)aryl, (un)substituted C1-8 alkoxy, amino, etc.; R2 = H, C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, HO(C1-8 alkyl); R3 = C1-8 alkyl, (un)substituted C2-8 alkenyl or alkynyl; (un)substituted cycloalkyl, heterocyclyl, (hetero)aryl, etc.; X = CO, C(:S), SO2] were prepared I and their pharmaceutically acceptable salts are selective kinase or dual-kinase inhibitors useful in the treatment of kinase-mediated disorders, especially as chemotherapeutic agents for treatment of cancer.

Thus,

adding DMF solution of 4-H2NSO2C6H4N:C:S at 0° to DMF solution of 1-amidino-3,5-dimethylpyrazole nitrate containing NaOH powder and stirring the mixture at 50-60° for 1 h gave the thiourea II. Stirring the latter vigorously with hydrazine for 2-3 h at 50-60° and N-acylating the resulting aminotriazole derivative with 2,6-F2C6H3COCl in pyridine gave a title compound III which inhibited enzymic activity of vascular endothelial growth factor receptor-2 with IC50 0.1062 μM.

ST aminotriazole prepn inhibitor kinase; triazolylaminobenzenesulfonamide amino difluorobenzoyl prepn kinase inhibitor; vascular endothelial growth factor receptor inhibitor triazolediamine deriv prepn

IT Alopecia

#### Angiogenesis

Antitumor agents

Blood vessel, disease

(preparation of triazolediamine derivs. as kinase inhibitors)

IT Vascular endothelial growth factor receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(preparation of triazolediamine derivs. as kinase inhibitors)

IT Artery, disease

(restenosis; preparation of triazolediamine derivs. as kinase inhibitors)

IT 98-88-4, Benzoyl chloride 393-52-2, 2-Fluorobenzoyl chloride 527-69-5, 2-Furoyl chloride 610-14-0, 2-Nitrobenzoyl chloride 933-88-0, 2-Methylbenzoyl chloride 938-18-1, 2,4,6-Trimethylbenzoyl chloride 1989-53-3, 2,6-Dimethoxybenzoyl chloride 4136-95-2, 2,4,6-Trichlorobenzoyl chloride 4659-45-4, 2,6-Dichlorobenzoyl chloride 18063-02-0, 2,6-Difluorobenzoyl chloride 60230-36-6, 2,6-Difluorobenzenesulfonyl chloride 72482-64-5, 2,4-Difluorobenzoyl chloride 79455-63-3, 2-Chloro-6-fluorobenzoyl chloride 109227-12-5, 2-Fluoro-6-(trifluoromethyl)benzoyl chloride 189807-20-3, 2,3,6-Trifluorobenzoyl chloride 261762-81-6 261763-39-7

- RL: RCT (Reactant); RACT (Reactant or reagent)  
(N-acylation of triazole derivative; preparation of triazolediamine derivs.  
as  
kinase inhibitors)
- IT 1455-77-2, 1H-1,2,4-Triazole-3,5-diamine 3310-68-7 37627-92-2  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(N-benzoylation; preparation of triazolediamine derivs. as kinase  
inhibitors)
- IT 18162-48-6, tert-Butyldimethylsilyl chloride  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(O-protection of difluorophenylethanol; preparation of triazolediamine  
derivs. as kinase inhibitors)
- IT 38184-47-3, 3,5-Dimethylpyrazole-1-carboxamidine nitrate  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(addition reaction with Ph isothiocyanate derivative; preparation of  
triazolediamine derivs. as kinase inhibitors)
- IT 103-71-9, Phenyl isocyanate, reactions 65295-69-4, 2,6-Difluorophenyl  
isocyanate 207974-17-2, 2,6-Difluorophenyl isothiocyanate  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(addition reaction with aminotriazole derivative; preparation of  
triazolediamine  
derivs. as kinase inhibitors)
- IT 7356-55-0 17614-69-6 223785-90-8 223785-92-0  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(addition reaction with carboxamidine derivative; preparation of  
triazolediamine  
derivs. as kinase inhibitors)
- IT 23861-85-0  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(addition reaction with pyrazolecarboxamidine derivative; preparation of  
triazolediamine derivs. as kinase inhibitors)
- IT 22906-75-8, 1-Amidino-3,5-dimethylpyrazole  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(addition with (aminosulfonyl)benzene isothiocyanate; preparation of  
triazolediamine derivs. as kinase inhibitors)
- IT 51908-29-3  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(addition with amidinodimethylpyrazole; preparation of triazolediamine  
derivs.  
as kinase inhibitors)
- IT 425-75-2, Ethyl trifluoromethanesulfonate  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(amidation of aminotriazole derivative; preparation of triazolediamine  
derivs.  
as kinase inhibitors)
- IT 55-22-1, Isonicotinic acid, reactions 59-67-6, Nicotinic acid, reactions  
88-13-1, Thiophene-3-carboxylic acid 98-89-5, Cyclohexanecarboxylic acid  
98-98-6, Picolinic acid 527-72-0, Thiophene-2-carboxylic acid  
632-46-2, 2,6-Dimethylbenzoic acid 1124-65-8, 3-(2-Thienyl)acrylic acid  
1460-16-8, Cycloheptanecarboxylic acid 1918-77-0, 2-Thiopheneacetic acid  
1918-79-2, 5-Methylthiophene-2-carboxylic acid 3400-45-1,  
Cyclopentanecarboxylic acid 4066-41-5, 5-Acetylthiophene-2-carboxylic  
acid 4100-13-4, 1,2,3-Thiadiazole-4-carboxylic acid 6314-28-9,  
Benzo[b]thiophene-2-carboxylic acid 7311-63-9, 5-Bromothiophene-2-  
carboxylic acid 7311-64-0, 3-Bromothiophene-2-carboxylic acid  
13064-83-0, trans-4-Methyl-1-cyclohexanecarboxylic acid 18212-21-0,  
4-Methyl-1,2,3-thiadiazole-5-carboxylic acid 21169-71-1,  
Isoxazole-5-carboxylic acid 23806-24-8, 3-Methylthiophene-2-carboxylic  
acid 29212-25-7, 5-tert-Butylthiophene-2-carboxylic acid 32431-84-8,  
3-Fluorothiophene-2-carboxylic acid 38289-28-0, trans-4-Butyl-1-  
cyclohexanecarboxylic acid 50901-18-3, 3-(Acetylamino)thiophene-2-  
carboxylic acid 53137-27-2, 2,4-Dimethylthiazole-5-carboxylic acid  
56586-13-1 59337-89-2, 3-Chlorothiophene-2-carboxylic acid 67595-44-2

74772-17-1 83141-10-0, 2,6-Difluoro-3-nitrobenzoic acid 85068-28-6,  
2,6;-Difluorophenylacetic acid 119082-97-2, 5-(2-Pyridyl)thiophene-2-  
carboxylic acid 139926-23-1, 3-Ethoxythiophene-2-carboxylic acid  
152152-09-5, 2,6-Difluorocinnamic acid 207866-53-3 225104-76-7,  
3-Chloro-2,6-difluorobenzoic acid

RL: RCT (Reactant); RACT (Reactant or reagent)  
(amidation of triazole derivative; preparation of triazolediamine derivs. as  
kinase inhibitors)

IT 144-83-2 2221-00-3, 4-Imidazol-1-ylaniline 6523-49-5 52761-74-7  
53250-82-1 77837-46-8 89518-99-0 90556-91-5

RL: RCT (Reactant); RACT (Reactant or reagent)  
(condensation with di-Ph cyanocarbonimide; preparation of triazolediamine  
derivs. as kinase inhibitors)

IT 79463-77-7, Diphenyl cyanocarbonimide

RL: RCT (Reactant); RACT (Reactant or reagent)  
(condensation with imidazolylaniline; preparation of triazolediamine derivs.  
as kinase inhibitors)

IT 150977-45-0, Vascular endothelial growth factor receptor-2 kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(inhibitors; preparation of triazolediamine derivs. as kinase inhibitors)

IT 443799-31-3P 443799-33-5P 443799-38-0P 443799-39-1P 443799-42-6P  
443799-46-0P 443799-47-1P 443799-52-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)

(preparation and N-benzoylation; preparation of triazolediamine derivs. as

kinase

inhibitors)

IT 443799-40-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)

(preparation and N-methylation; preparation of triazolediamine derivs. as

kinase

inhibitors)

IT 443799-49-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)

(preparation and amidation with dimethylthiophenecarboxylic acid;

preparation of

triazolediamine derivs. as kinase inhibitors)

IT 443799-45-9P 443799-48-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)

(preparation and amidation with ethylthiophenecarboxylic acid; preparation

of

triazolediamine derivs. as kinase inhibitors)

IT 443799-50-6P 443799-51-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)

(preparation and amidation with methylthiophenecarboxylic acid; preparation

of

triazolediamine derivs. as kinase inhibitors)

IT 443799-44-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)

(preparation and amidation with thiophenecarboxylic acid derivative;

preparation of

triazolediamine derivs. as kinase inhibitors)

IT 23229-72-3P, 5-Ethyl-2-thiophenecarboxylic acid 65613-27-6P,  
3,5-Dimethyl-2-thiophenecarboxylic acid 443799-35-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)

(preparation and amidation with triazole derivative; preparation of

triazolediamine

derivs. as kinase inhibitors)

IT 443799-36-8P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation and deprotection; preparation of triazolediamine derivs. as kinase inhibitors)

IT 443799-30-2P 443799-32-4P 443799-37-9P 443799-41-5P 443799-43-7P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation and reaction with hydrazine; preparation of triazolediamine derivs. as kinase inhibitors)

IT 2267-47-2P, Benzenemethanol, 2,4-difluoro- $\alpha$ -methyl-  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation and silylation; preparation of triazolediamine derivs. as kinase inhibitors)

IT 134549-83-0, Protein kinase 347147-98-2, Receptor protein kinase  
 372092-80-3, Protein kinase  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (preparation of triazolediamine derivs. as kinase inhibitors)

IT 324074-12-6P 324074-15-9P 324074-30-8P 443797-96-4P 443797-97-5P  
 443797-98-6P 443797-99-7P 443798-00-3P 443798-01-4P 443798-02-5P  
 443798-03-6P 443798-04-7P 443798-05-8P 443798-06-9P 443798-07-0P  
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 443798-13-8P 443798-14-9P 443798-15-0P 443798-16-1P 443798-17-2P  
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 443798-23-0P 443798-24-1P 443798-25-2P 443798-26-3P 443798-27-4P  
 443798-28-5P 443798-29-6P 443798-30-9P 443798-31-0P 443798-32-1P  
 443798-33-2P 443798-34-3P 443798-35-4P 443798-36-5P 443798-37-6P  
 443798-38-7P 443798-39-8P 443798-40-1P 443798-41-2P 443798-42-3P  
 443798-43-4P 443798-44-5P 443798-45-6P 443798-46-7P 443798-47-8P  
 443798-48-9P 443798-49-0P 443798-50-3P 443798-51-4P 443798-52-5P  
 443798-53-6P 443798-54-7P 443798-55-8P 443798-56-9P  
 443798-57-0P 443798-58-1P 443798-59-2P 443798-60-5P 443798-61-6P  
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 443798-82-1P 443798-83-2P 443798-84-3P 443798-85-4P 443798-86-5P  
 443798-87-6P 443798-88-7P 443798-89-8P 443798-90-1P 443798-91-2P  
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 443799-02-8P 443799-03-9P 443799-04-0P 443799-05-1P 443799-06-2P  
 443799-07-3P 443799-08-4P 443799-09-5P 443799-10-8P 443799-12-0P  
 443799-14-2P 443799-16-4P 443799-18-6P 443799-20-0P 443799-22-2P  
 443799-24-4P 443799-25-5P 443799-26-6P 443799-27-7P 443799-28-8P  
 443799-29-9P  
 RL: BUU (Biological use, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of triazolediamine derivs. as kinase inhibitors)

IT 443799-53-9  
 RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)  
 (preparation of triazolediamine derivs. as kinase inhibitors)

IT 443799-34-6P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation, lithiation and carboxylation; preparation of triazolediamine derivs. as kinase inhibitors)

IT 364-83-0, 2',4'-Difluoroacetophenone

RL: RCT (Reactant); RACT (Reactant or reagent)

(reduction to alc.; preparation of triazolediamine derivs. as kinase inhibitors)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Du Pont; GB 1065964 A 1967
- (2) Gaetano, D; US 2352944 A 1944 HCAPLUS
- (3) Glynn, S; WO 0109106 A 2001 HCAPLUS
- (4) Green Cross Corp; EP 0710654 A 1996 HCAPLUS
- (5) Song, C; WO 9921845 A 1999 HCAPLUS

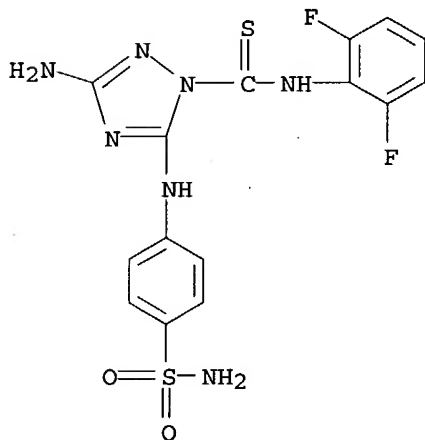
IT 443798-55-8P

RL: BUU (Biological use, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of triazolediamine derivs. as kinase inhibitors)

RN 443798-55-8 HCAPLUS

CN 1H-1,2,4-Triazole-1-carbothioamide, 3-amino-5-[[4-(aminosulfonyl)phenyl]amino]-N-(2,6-difluorophenyl)- (9CI) (CA INDEX NAME)



L108 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2000:881129 HCAPLUS

DN 134:42135

ED Entered STN: 15 Dec 2000

TI Preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases.

IN Salituro, Francesco; Bemis, Guy; Green, Jeremy; Fejzo, Jasna; Xie, Xiaoling

PA Vertex Pharmaceuticals Incorporated, USA

SO PCT Int. Appl., 37 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07D239-54

ICS C07D401-12; A61K031-505; C07D401-12; C07D239-00; C07D213-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))

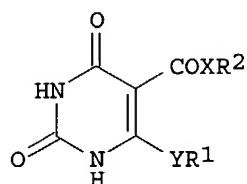
Section cross-reference(s): 1

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000075118	A1	20001214	WO 2000-US15248	20000602 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,				

LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD,  
 SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,  
 ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,  
 CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2003100549 A1 20030529 US 2001-8277 20011203 <--  
 PRAI US 1999-137523P P 19990603 <--  
 WO 2000-US15248 A1 20000602 <--  
 OS MARPAT 134:42135  
 GI



AB Title compds. [I; Y = O, NH, NR, S, SO, SO<sub>2</sub>; X = O, NH, NR; R<sub>1</sub>, R<sub>2</sub> = H, (substituted) alkyl, alkenyl, (aromatic) (bicyclic) carbocyclyl, heterocyclyl; R = alkyl, alkenyl, (aromatic) (bicyclic) carbocyclyl, heterocyclyl], were prepared as inhibitors of c-JUN N-terminal kinases. Thus, I (R<sub>1</sub>Y, R<sub>2</sub>X = PhNH) inhibited JNK3 with IC<sub>50</sub> <1 μM.

ST pyrimidinedione prepn jnk inhibitor; antiinflammatory pyrimidinedione; autoimmune disease treatment pyrimidinedione; bone disorder treatment pyrimidinedione; infectious disease treatment pyrimidinedione; neurodegenerative disease treatment pyrimidinedione; allergy inhibitor pyrimidinedione

IT Intestine, disease  
 (Crohn's, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Nervous system  
 (Huntington's chorea, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Sarcoma  
 (Kaposi's, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Respiratory distress syndrome  
 (adult, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Nervous system  
 (amyotrophic lateral sclerosis, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Dermatitis  
 (atopic, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Heart, disease  
 (attack, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Stomach, disease  
 (autoimmune gastritis, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Nervous system  
 (degeneration, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Kidney, disease

(glomerulonephritis, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Transplant and Transplantation  
(graft-vs.-host reaction, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Anemia (disease)  
(hemolytic, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Heart, disease  
(hypertrophy, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Intestine, disease  
(inflammatory, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Reperfusion  
(injury, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Brain, disease  
(ischemia, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Antitumor agents  
(leukemia; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT **Angiogenesis**  
(neovascularization, treatment or ocular neovascularization; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Agranulocytosis  
(neutropenia, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Pancreas, disease  
(pancreatitis, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Allergy inhibitors  
Anti-Alzheimer's agents  
Anti-inflammatory agents  
Antiarthritics  
Antiasthmatics  
Antidiabetic agents  
Antiparkinsonian agents  
Antitumor agents  
Bone, disease  
Platelet aggregation inhibitors  
(preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Connective tissue  
(scleroderma, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Brain, disease  
(stroke, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Osteoporosis  
(therapeutic agents; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Platelet (blood)  
(thrombocytopenia, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Thyroid gland, disease  
(thyroiditis, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Cytokines  
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)  
(treatment of disorders associated with proinflammatory cytokines; preparation

of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT **Angiogenesis**  
Cell proliferation  
(treatment of disorders; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Immunity  
(treatment of pathol. immune response; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Hyperplasia  
(treatment of vascular hyperplasia; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Autoimmune disease  
Graves' disease  
Hepatitis  
Hypoxia, animal  
Infection  
Lupus erythematosus  
Melanoma  
Multiple myeloma  
Multiple sclerosis  
Myasthenia gravis  
Psoriasis  
(treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT Intestine, disease  
(ulcerative colitis, treatment; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT 289898-51-7, c-JUN N-terminal kinase  
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)  
(inhibitors; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT 264884-33-5 312752-09-3 312752-10-6  
312752-12-8 312752-13-9 312752-15-1  
312752-17-3 312752-19-5 312752-21-9  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT 62-53-3, Aniline, reactions 108-59-8, Dimethyl malonate 10191-60-3, Dimethyl N-cyanodithioiminocarbonate  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT 136411-38-6P 312752-23-1P 312752-24-2P 312752-25-3P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

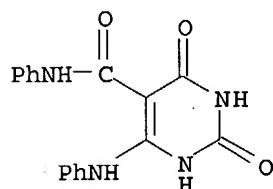
(1) Allison; Immunopharmacology 2000, V47(2-3), P63 HCAPLUS  
(2) Bell; J Heterocycl Chem 1983, V20(1), P41 HCAPLUS  
(3) Bellon, S; WO 9958502 A 1999 HCAPLUS  
(4) Bemis, G; WO 9964400 A 1999 HCAPLUS  
(5) Brewer, A; US 4920126 A 1990 HCAPLUS  
(6) Iordanov; Mol Cell Biol 1997, V17(6), P3373 HCAPLUS  
(7) Lamon; Tetrahedron Lett 1970, 45, P3957 HCAPLUS  
(8) Supko; J Liq Chromatogr 1991, V14(11), P2169 HCAPLUS  
(9) Tominaga; J Heterocycl Chem 1991, V28(4), P1039 HCAPLUS  
(10) Wang, Z; Structure 1998, V6(9), P1117 HCAPLUS

IT 264884-33-5  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

RN 264884-33-5 HCAPLUS

CN 5-Pyrimidinecarboxamide, 1,2,3,4-tetrahydro-2,4-dioxo-N-phenyl-6-(phenylamino)- (9CI) (CA INDEX NAME)



=> d all fhitstr tot l112

L112 ANSWER 1 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:256049 HCAPLUS

DN 136:257237

ED Entered STN: 05 Apr 2002

TI Tumor cell killing by cell cycle checkpoint abrogation combined with inhibition of the "classical" mitogen activated protein (MAP) kinase pathway

IN Dent, Paul; Grant, Steven; McKinstry, Robert; Dai, Yum

PA Virginia Commonwealth University, USA

SO PCT Int. Appl., 67 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-55

ICS A61K031-335; A01N043-02

CC 1-6 (Pharmacology)

Section cross-reference(s): 8

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002026236	A1	20020404	WO 2001-US30508	20010928 <--
	WO 2002026236	C2	20030220		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRAI US 2000-235938P P 20000928 <--

AB The present invention provides a method for treating cancer by promoting apoptosis and reducing clonogenic survival of cancer cells. The method encompasses co-administering 1) a cell cycle checkpoint abrogation agent (for example, UCN-01 or caffeine) and 2) an inhibitor of a compensatory cytoprotective pathway, such as an agent that inhibits the MEK 1/2 pathway (e.g.; PD98059, U0126, or PD184352) or an agent that inhibits the PI 3 pathway (e.g.; LY294002 or wortmanin). In addition, because the co-administration step also radiosensitizes cancer cells, the method addnl. encompasses the administration of radiation to further reduce clonogenic survival of cancer cells. The method promotes apoptosis and reduces clonogenic survival in many types of cancer cells, including leukemia cells, prostate cancer cells, breast cancer cells, myeloma cells,

and lymphoma cells.

- ST antitumor cell cycle checkpoint abrogation MAP kinase; radiosensitizer  
tumor apoptosis MAP kinase
- IT Proteins  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(Bax; tumor cell killing by cell cycle checkpoint abrogation combined  
with inhibition of MAP kinase pathway)
- IT Proteins  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(Bcl-2; tumor cell killing by cell cycle checkpoint abrogation combined  
with inhibition of MAP kinase pathway)
- IT Proteins  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(Bcl-xL; tumor cell killing by cell cycle checkpoint abrogation  
combined with inhibition of MAP kinase pathway)
- IT Transcription factors  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(CREB (cAMP-responsive element-binding); tumor cell killing by cell  
cycle checkpoint abrogation combined with inhibition of MAP kinase  
pathway)
- IT Proteins  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(XIAP (X-linked inhibitor of apoptosis protein); tumor cell killing by  
cell cycle checkpoint abrogation combined with inhibition of MAP kinase  
pathway)
- IT Antitumor agents  
(brain; tumor cell killing by cell cycle checkpoint abrogation combined  
with inhibition of MAP kinase pathway)
- IT Antitumor agents  
(carcinoma; tumor cell killing by cell cycle checkpoint abrogation  
combined with inhibition of MAP kinase pathway)
- IT Intestine, neoplasm  
(colon, inhibitors; tumor cell killing by cell cycle checkpoint  
abrogation combined with inhibition of MAP kinase pathway)
- IT Antitumor agents  
(colon; tumor cell killing by cell cycle checkpoint abrogation combined  
with inhibition of MAP kinase pathway)
- IT Liver, neoplasm  
(hepatoma, inhibitors; tumor cell killing by cell cycle checkpoint  
abrogation combined with inhibition of MAP kinase pathway)
- IT Antitumor agents  
(hepatoma; tumor cell killing by cell cycle checkpoint abrogation  
combined with inhibition of MAP kinase pathway)
- IT Brain, neoplasm  
(inhibitors; tumor cell killing by cell cycle checkpoint abrogation  
combined with inhibition of MAP kinase pathway)
- IT Antitumor agents  
(leukemia; tumor cell killing by cell cycle checkpoint abrogation  
combined with inhibition of MAP kinase pathway)
- IT Antitumor agents  
(lymphoma; tumor cell killing by cell cycle checkpoint abrogation  
combined with inhibition of MAP kinase pathway)
- IT Antitumor agents  
(mammary gland; tumor cell killing by cell cycle checkpoint abrogation  
combined with inhibition of MAP kinase pathway)
- IT Mitochondria  
(membrane potential; tumor cell killing by cell cycle checkpoint  
abrogation combined with inhibition of MAP kinase pathway)
- IT Leukemia  
(monocytic; tumor cell killing by cell cycle checkpoint abrogation  
combined with inhibition of MAP kinase pathway)
- IT Antitumor agents  
(myeloma; tumor cell killing by cell cycle checkpoint abrogation

combined with inhibition of MAP kinase pathway)

IT Mammary gland  
Prostate gland  
(neoplasm, inhibitors; tumor cell killing by cell cycle checkpoint abrogation combined with inhibition of MAP kinase pathway)

IT Cyclin dependent kinase inhibitors  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(p21CIP1; tumor cell killing by cell cycle checkpoint abrogation combined with inhibition of MAP kinase pathway)

IT Cyclin dependent kinase inhibitors  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(p27KIP1; tumor cell killing by cell cycle checkpoint abrogation combined with inhibition of MAP kinase pathway)

IT Antitumor agents  
(prostate gland; tumor cell killing by cell cycle checkpoint abrogation combined with inhibition of MAP kinase pathway)

IT Antitumor agents  
Apoptosis  
Cell cycle  
Cell proliferation  
Radiosensitizers, biological  
Radiotherapy  
(tumor cell killing by cell cycle checkpoint abrogation combined with inhibition of MAP kinase pathway)

IT 9007-43-6, Cytochrome c, biological studies 115926-52-8, PI 3 kinase  
137632-07-6, ERK1 protein kinase 137632-08-7, ERK2 protein kinase  
140208-22-6, Cdc25C phosphatase 141436-78-4, Protein kinase C  
142243-02-5, MAP kinase 142805-58-1, MEK-1 kinase 143375-65-9, Cdc2 kinase 150316-14-6, MEK2 kinase 155215-87-5, JNK kinase 165245-96-5, p38 Kinase 179241-78-2, Caspase 8 180189-96-2, Caspase 9  
186322-81-6, Caspase 201556-11-8, Procaspace 3 201556-15-2, Procaspace 8 208778-60-3, Procaspace 9  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(tumor cell killing by cell cycle checkpoint abrogation combined with inhibition of MAP kinase pathway)

IT 112953-11-4, UCN-01 154447-36-6, LY 294002  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(tumor cell killing by cell cycle checkpoint abrogation combined with inhibition of MAP kinase pathway)

IT 58-08-2, Caffeine, biological studies 19545-26-7, Wortmannin  
109511-58-2, U 126 167869-21-8, PD 98059 212631-79-3, PD 184352 305350-87-2, SL 327  
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(tumor cell killing by cell cycle checkpoint abrogation combined with inhibition of MAP kinase pathway)

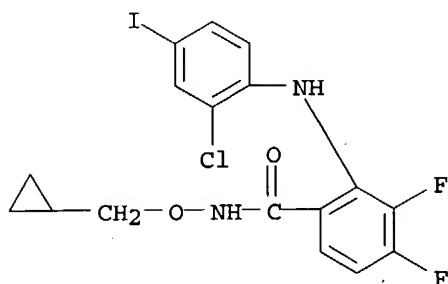
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE  
(1) Dai, Y; Cancer Res 2001, V61, P5106 HCAPLUS  
(2) Daoud, S; US 6214821 B1 2001 HCAPLUS  
(3) Deng; PNAS 2000, V97(4), P1578 HCAPLUS  
(4) Dent; US 6147107 A 2000 HCAPLUS  
(5) Sebolt-Leopold; Nat Med 1999, V5(7), P810 HCAPLUS

IT 212631-79-3, PD 184352  
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(tumor cell killing by cell cycle checkpoint abrogation combined with inhibition of MAP kinase pathway)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 2 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:171716 HCAPLUS

DN 136:210554

ED Entered STN: 08 Mar 2002

TI Inhibition of mitogen-activated protein kinase (MAPK) pathway as selective therapeutic strategy against melanoma

IN Vande Woude, George

PA Van Andel Institute, USA; Koo, Han-Mo

SO PCT Int. Appl., 76 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K038-00

CC 1-6 (Pharmacology)

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002017952	A2	20020307	WO 2001-US27063	20010831 <--
	WO 2002017952	A3	20030424		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	AU 2001088562	A5	20020313	AU 2001-88562	20010831 <--
	US 2002054869	A1	20020509	US 2001-942940	20010831 <--
	EP 1365796	A2	20031203	EP 2001-968307	20010831 <--
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
PRAI	US 2000-229290P	P	20000901	<--	
	US 2001-285690P	P	20010424		
	WO 2001-US27063	W	20010831		
AB	Inhibitors of the MAPK pathway, including MEK-directed proteases and small mol. inhibitors, are cytotoxic to human melanoma cells in vitro and in vivo via apoptotic mechanisms. These compds. are used to kill melanoma cells and to treat subjects with melanoma, either alone or in combination with other therapeutic modalities.				
ST	melanoma treatment MAPK inhibitor; mitogen activated protein kinase inhibitor melanoma treatment; MEK directed protease melanoma treatment				
IT	Proteins				
	RL: PAC (Pharmacological activity); BIOL (Biological study) (Bacillus anthracis edema factor; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)				
IT	Animal cell line (LOX-IMVI; MAPK pathway inhibitors as selective therapeutic strategy				

against melanoma)

IT Animal cell line  
(M14; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Animal cell line  
(M19-MEL; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Animal cell line  
(MALME-3M; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Apoptosis  
Cell cycle  
Human  
Signal transduction, biological  
(MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Melanins  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Animal cell line  
(SK-MEL-28; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Animal cell line  
(SK-MEL-2; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Animal cell line  
(SK-MEL-5; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Animal cell line  
(UACC-257; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Animal cell line  
(UACC-62; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Toxins  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(anthrax lethal factor; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Toxins  
RL: PAC (Pharmacological activity); BIOL (Biological study)  
(anthrax protective antigen; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Antitumor agents  
(central nervous system; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Nervous system  
(central, neoplasm, inhibitors; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Intestine, neoplasm  
(colon, inhibitors; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Antitumor agents  
(colon; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Kidney, neoplasm  
Ovary, neoplasm  
(inhibitors; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Antitumor agents  
(kidney; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Bacillus anthracis  
(lethal factor; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Antitumor agents  
(leukemia; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Antitumor agents  
(lung non-small-cell carcinoma; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Antitumor agents  
(mammary gland; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Antitumor agents  
(melanoma; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Mammary gland  
Prostate gland  
(neoplasm, inhibitors; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Lung, neoplasm  
(non-small-cell carcinoma, inhibitors; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Antitumor agents  
(ovary; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Antitumor agents  
(prostate gland; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT Drug interactions  
(synergistic; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT 137632-07-6, ERK1 kinase 137632-08-7, ERK2 kinase 142243-02-5,  
Mitogen-activated protein kinase  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT 28822-58-4, IBMX  
RL: PAC (Pharmacological activity); BIOL (Biological study)  
(MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT 96251-59-1, DX-52-1 109511-58-2, U0126 167869-21-8, PD98059  
212631-79-3, PD184352  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

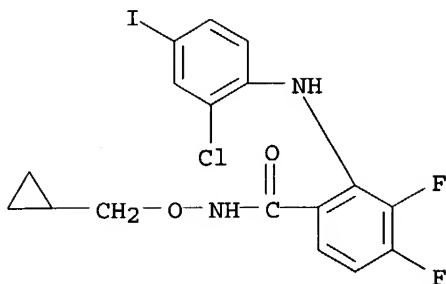
IT 142805-58-1, MEK kinase  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(MEK-directed protease; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT 9001-92-7, Protease  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(MEK-directed; MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

IT 212631-79-3, PD184352  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(MAPK pathway inhibitors as selective therapeutic strategy against melanoma)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 3 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:747038 HCAPLUS

DN 135:283170

ED Entered STN: 12 Oct 2001

TI Use of MEK inhibitors for the production of medicaments against DNA and RNA viruses

IN Ludwig, Stephan; Pleschka, Stephan

PA Transmit Gesellschaft fuer Technologietransfer MbH, Germany

SO Ger. Offen., 6 pp.

CODEN: GWXXBX

DT Patent

LA German

IC ICM A61K031-352

CC 1-5 (Pharmacology)

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10017480	A1	20011011	DE 2000-10017480	20000407 <--
WO 2001076570	A2	20011018	WO 2001-DE1292	20010405 <--
WO 2001076570	A3	20020510		
W: AU, CA, CN, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1274421	A2	20030115	EP 2001-935945	20010405 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2004505891	T2	20040226	JP 2001-574088	20010405 <--
US 2003060469	A1	20030327	US 2002-240904	20021004 <--
DE 2000-10017480	A	20000407	<--	
WO 2001-DE1292	W	20010405		

AB The invention provides MEK-inhibitors (e.g. U0126) for the production of medicaments for prophylaxis and antiviral therapy against DNA and RNA viruses, especially against intranuclear replicating neg. strand RNA viruses, e.g. influenza virus or Borna disease virus.

ST MEK inhibitor antiviral RNA DNA virus; U0126 antiviral RNA DNA virus;  
influenza virus antiviral MEK inhibitor; Borna disease virus antiviral MEK  
inhibitor

IT    Antiviral agents  
      Borna disease virus  
      DNA viruses  
      Influenza A virus  
      Influenza virus  
      RNA viruses

(MEK inhibitors for production of medicaments against DNA and RNA viruses)

IT Drug delivery systems  
(prodrugs; MEK inhibitors for production of medicaments against DNA and RNA viruses)

IT 109511-58-2 109511-58-2D, derivs. 167869-21-8 167869-21-8D, derivs.

212631-79-3 212631-79-3D, derivs.

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(MEK inhibitors for production of medicaments against DNA and RNA viruses)

IT 142805-58-1, MEK kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(MEK inhibitors for production of medicaments against DNA and RNA viruses)

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Anon; WO 0042003 A1 HCAPLUS

(2) Anon; WO 0042029 A1 HCAPLUS

(3) Anon; WO 9837881 A1 HCAPLUS

(4) Chen, W; Experimental Lung Research 2000, V26, PS13

(5) Rodems, S; Journal Of Virology 1998, V72(11), PS9173

(6) Tang, P; Infection And Immunity 1998, V66(3), PS1106

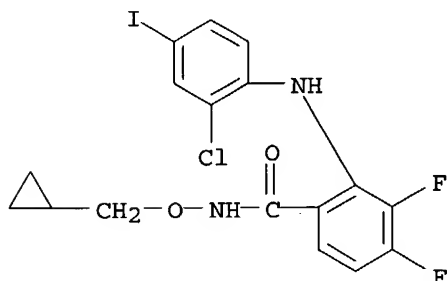
IT 212631-79-3

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(MEK inhibitors for production of medicaments against DNA and RNA viruses)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 4 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:689470 HCAPLUS

DN 136:48126

ED Entered STN: 20 Sep 2001

TI Therapeutic targeting of the MEK/MAPK signal transduction module in acute myeloid leukemia

AU Milella, Michele; Kornblau, Steven M.; Estrov, Zeev; Carter, Bing Z.; Lapillonne, Helene; Harris, David; Konopleva, Marina; Zhao, Shourong; Estey, Elihu; Andreeff, Michael

CS Department of Blood and Marrow Transplantation, Section of Molecular Hematology and Therapy, The University of Texas, M.D. Anderson Cancer Center, Houston, TX, 77030, USA

SO Journal of Clinical Investigation (2001), 108(6), 851-859  
CODEN: JCINAO; ISSN: 0021-9738

PB American Society for Clinical Investigation

DT Journal

LA English

CC 1-6 (Pharmacology)

AB The mitogen-activated protein kinase (MAPK) pathway regulates growth and survival of many cell types, and its constitutive activation has been implicated in the pathogenesis of a variety of malignancies. In this study we demonstrate that small-mol. MEK inhibitors (PD98059 and PD184352) profoundly impair cell growth and survival of acute myeloid leukemia (AML) cell lines and primary samples with constitutive MAPK activation. These

agents abrogate the clonogenicity of leukemic cells but have minimal effects on normal hematopoietic progenitors. MEK blockade also results in sensitization to spontaneous and drug-induced apoptosis. At a mol. level, these effects correlate with modulation of the expression of cyclin-dependent kinase inhibitors (p27Kip1 and p21Waf1/CIP1) and antiapoptotic proteins of the inhibitor of apoptosis proteins (IAP) and Bcl-2 families. Interruption of constitutive MEK/MAPK signaling therefore represents a promising therapeutic strategy in AML.

- ST acute myeloid leukemia inhibitor PD98059 PD184352; MEK MAPK signal transduction antileukemia apoptosis
- IT Proteins  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (Bcl-2; therapeutic targeting of MEK/MAPK signal transduction module in acute myeloid leukemia)
- IT Proteins  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (IAP (inhibitor of apoptosis proteins); therapeutic targeting of MEK/MAPK signal transduction module in acute myeloid leukemia)
- IT Leukemia  
(acute myelogenous, inhibitor; therapeutic targeting of MEK/MAPK signal transduction module in acute myeloid leukemia)
- IT Apoptosis  
Hematopoietic precursor cell  
Signal transduction, biological  
(therapeutic targeting of MEK/MAPK signal transduction module in acute myeloid leukemia)
- IT Cyclin dependent kinase inhibitors  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (therapeutic targeting of MEK/MAPK signal transduction module in acute myeloid leukemia)
- IT 142805-58-1, Mek  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (therapeutic targeting of MEK/MAPK signal transduction module in acute myeloid leukemia)
- IT 167869-21-8, PD98059 212631-79-3, PD184352  
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);  
USES (Uses)  
(therapeutic targeting of MEK/MAPK signal transduction module in acute myeloid leukemia)

RE.CNT 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Alessi, D; J Biol Chem 1995, V270, P27489 HCAPLUS
- (2) Andreeff, M; Leukemia 1999, V13, P1881 HCAPLUS
- (3) Blalock, W; Leukemia 2000, V14, P1080 HCAPLUS
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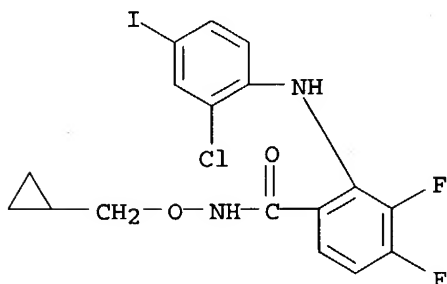
IT 212631-79-3, PD184352

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(therapeutic targeting of MEK/MAPK signal transduction module in acute myeloid leukemia)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 5 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:633080 HCAPLUS

DN 136:63675

ED Entered STN: 31 Aug 2001

TI MEK1/2 inhibitors promote ara-C-induced apoptosis but not loss of ΔΨm in HL-60 cells

AU Yu, Chunrong; Wang, Zhiliang; Dent, Paul; Grant, Steven

CS Department of Medicine, Virginia Commonwealth University, Richmond, VA, 23298, USA

SO Biochemical and Biophysical Research Communications (2001), 286(5), 1011-1018

CODEN: BBRC99; ISSN: 0006-291X

PB Academic Press

DT Journal

LA English

CC 1-6 (Pharmacology)

- AB The effects of pharmacol. MEK1/2 inhibitors on ara-C-mediated mitochondrial injury, caspase activation, and apoptosis have been examined in HL-60 leukemic cells. Coadministration of subtoxic concns. of the MEK1/2 inhibitors U0126 (20  $\mu$ M), PD98059 (40  $\mu$ M), or PD184352 (10  $\mu$ M) with 10-100  $\mu$ M ara-C (6 h) potentiated apoptosis (i.e., by approx. twofold), and pro-caspase 3, pro-caspase 8, Bid, and PARP cleavage. Unexpectedly, MEK1/2 inhibitors failed to enhance ara-C-mediated loss of mitochondrial membrane potential ( $\Delta\Psi_m$ ), but instead induced substantial increases in cytosolic release of cytochrome c and Smac/DIABLO. U0126/ara-C-mediated apoptosis and pro-caspase 3 activation, but not cytochrome c or Smac/DIABLO release, were blocked by the pan-caspase inhibitor ZVAD-fmk. Together, these findings indicate that potentiation of ara-C-mediated lethality in HL-60 cells by MEK1/2 inhibitors involves enhanced cytosolic release of cytochrome c and Smac/DIABLO but not discharge of  $\Delta\Psi_m$ , implicating activation of an apoptotic pathway that differs, at least with respect to the nature of the accompanying mitochondrial injury, from that triggered by ara-C alone. (c) 2001 Academic Press.
- ST MEK1 inhibitor ara C leukemia apoptosis mechanism
- IT Proteins  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (Bid; pathway by which MEK1/2 inhibitors promote ara-C-induced apoptosis in HL-60 cells)
- IT Proteins  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (DIABLO; pathway by which MEK1/2 inhibitors promote ara-C-induced apoptosis in HL-60 cells)
- IT Apoptosis  
(MEK1/2 inhibitors promote ara-C-induced apoptosis but not loss of  $\Delta\Psi_m$  in HL-60 cells)
- IT Membrane potential  
(biol., mitochondrial; MEK1/2 inhibitors promote ara-C-induced apoptosis but not loss of  $\Delta\Psi_m$  in HL-60 cells)
- IT Mitochondria  
(injury; MEK1/2 inhibitors promote ara-C-induced apoptosis but not loss of  $\Delta\Psi_m$  in HL-60 cells)
- IT Antitumor agents  
(leukemia; MEK1/2 inhibitors promote ara-C-induced apoptosis but not loss of  $\Delta\Psi_m$  in HL-60 cells)
- IT Mitochondria  
(membrane, potential; MEK1/2 inhibitors promote ara-C-induced apoptosis but not loss of  $\Delta\Psi_m$  in HL-60 cells)
- IT Membrane, biological  
(mitochondrial, potential; MEK1/2 inhibitors promote ara-C-induced apoptosis but not loss of  $\Delta\Psi_m$  in HL-60 cells)
- IT 142805-58-1, MEK-1 kinase 150316-14-6, MEK2 kinase  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (MEK1/2 inhibitors promote ara-C-induced apoptosis but not loss of  $\Delta\Psi_m$  in HL-60 cells)
- IT 147-94-4, Ara C 109511-58-2, U0126 167869-21-8, PD98059 212631-79-3, PD184352  
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(MEK1/2 inhibitors promote ara-C-induced apoptosis but not loss of  $\Delta\Psi_m$  in HL-60 cells)
- IT 9055-67-8, Poly(ADP-ribose) polymerase  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (cleavage; pathway by which MEK1/2 inhibitors promote ara-C-induced apoptosis in HL-60 cells)
- IT 9007-43-6, Cytochrome c, biological studies 201556-11-8, Pro-caspase 3 201556-15-2, Pro-caspase 8  
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(pathway by which MEK1/2 inhibitors promote ara-C-induced apoptosis in  
HL-60 cells)

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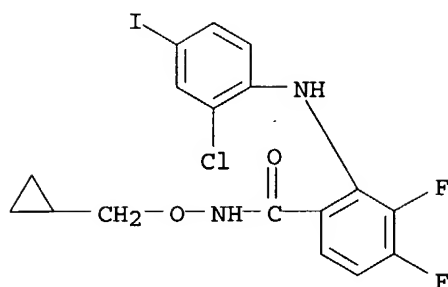
IT 212631-79-3, PD184352

RL: DMA (Drug mechanism of action); PAC (Pharmacological  
activity); THU (Therapeutic use); BIOL (Biological study);  
USES (Uses)

(MEK1/2 inhibitors promote ara-C-induced apoptosis but not loss of  
 $\Delta\psi_m$  in HL-60 cells)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-  
difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 6 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN  
 AN 2001:563138 HCAPLUS  
 DN 135:353156  
 ED Entered STN: 03 Aug 2001  
 TI Effects of MAP kinase cascade inhibitors on the MKK5/ERK5 pathway  
 AU Mody, N.; Leitch, J.; Armstrong, C.; Dixon, J.; Cohen, P.  
 CS Medical Research Council Protein Phosphorylation Unit, School of Life Sciences, MSI/WTB Complex, University of Dundee, Dundee, DD1 5EH, UK  
 SO FEBS Letters (2001), 502(1,2), 21-24  
 CODEN: FEBLAL; ISSN: 0014-5793  
 PB Elsevier Science B.V.  
 DT Journal  
 LA English  
 CC 2-10 (Mammalian Hormones)  
 Section cross-reference(s): 1  
 AB Antibodies that recognize the active phosphorylated forms of mitogen-activated protein kinase (MAPK) kinase 5 (MKK5) and extracellular signal-regulated kinase 5 (ERK5) in untransfected cells have been exploited to show that the epidermal growth factor (EGF)-induced activation of MKK5 and ERK5 occurs subsequent to the activation of ERK1 and ERK2 in HeLa cells. The drugs U0126 and PD184352, which prevent the activation of MKK1 (and hence the activation of ERK1/ERK2), also prevent the activation of MKK5, although higher concns. are required. Our studies define physiol. targets of the MKK5/ERK5 pathway as proteins whose phosphorylation is largely prevented by 10  $\mu$ M PD184352, but unaffected by 2  $\mu$ M PD184352. Surprisingly, 2  $\mu$ M PD184352 prolongs the activation of MKK5 and ERK5 induced by EGF or H2O2, indicating neg. control of the MKK5/ERK5 pathway by the classical MAPK cascade. Our results also indicate that ERK5 is not a significant activator of MAPK-activated protein kinase-1/RSK in HeLa cells.  
 ST MAP kinase cascade inhibitor MKK5 ERK5 pathway; EGF MKK5 ERK5 activation  
 MAP kinase cascade inhibitor  
 IT Signal transduction, biological  
 (effects of MAP kinase cascade inhibitors on MKK5/ERK5 pathway)  
 IT Phosphorylation, biological  
 (protein; effects of MAP kinase cascade inhibitors on MKK5/ERK5 pathway)  
 IT 62229-50-9, Epidermal growth factor  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (-induced activation of MKK5 and ERK5; effects of MAP kinase cascade inhibitors on MKK5/ERK5 pathway)  
 IT 90698-26-3 90698-26-3, RSK kinase  
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (ERK5 is not a significant activator of MAPK-activated protein kinase-1/RSK in HeLa cells)  
 IT 137632-07-6, Protein kinase ERK1 137632-08-7, Protein kinase ERK2

170347-45-2, Protein kinase ERK5 327046-95-7, Mitogen-activated protein kinase kinase 5

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(effects of MAP kinase cascade inhibitors on MKK5/ERK5 pathway)

IT 109511-58-2, U0126 212631-79-3, PD184352

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(effects of MAP kinase cascade inhibitors on MKK5/ERK5 pathway)

RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD

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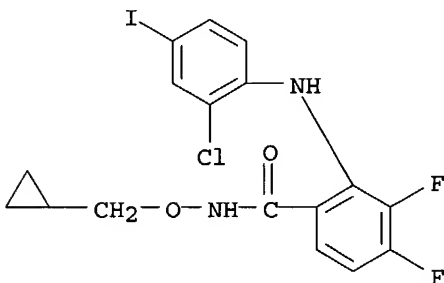
IT 212631-79-3, PD184352

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(effects of MAP kinase cascade inhibitors on MKK5/ERK5 pathway)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 7 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:503995 HCAPLUS

DN 135:298300

ED Entered STN: 12 Jul 2001

TI Pharmacological inhibitors of the mitogen-activated protein kinase (MAPK) kinase/MAPK cascade interact synergistically with UCN-01 to induce mitochondrial dysfunction and apoptosis in human leukemia cells

AU Dai, Yun; Yu, Chunrong; Singh, Victor; Tang, Lin; Wang, Zhiliang; McInistry, Robert; Dent, Paul; Grant, Steven

CS Division of Hematology/Oncology, Medical College of Virginia, Richmond, VA, 23298, USA

SO Cancer Research (2001), 61(13), 5106-5115

CODEN: CNREA8; ISSN: 0008-5472

PB American Association for Cancer Research

DT Journal

LA English

CC 1-6 (Pharmacology)

AB Interactions between the checkpoint abrogator UCN-01 and several pharmacol. inhibitors of the mitogen-activated protein kinase (MAPK) kinase (MEK)/MAPK pathway have been examined in a variety of human leukemia cell lines. Exposure of U937 monocytic leukemia cells to a marginally toxic concentration of UCN-01 (e.g., 150 nM) for 18 h resulted in phosphorylation/activation of p42/44 MAPK. Coadministration of the MEK inhibitor PD184352 (10  $\mu$ M) blocked UCN-01-induced MAPK activation and was accompanied by marked mitochondrial damage (e.g., cytochrome c release and loss of  $\Delta\psi_m$ ), caspase activation, DNA fragmentation, and apoptosis. Similar interactions were noted in the case of other MEK inhibitors (e.g., PD98059; U0126) as well as in multiple other leukemia cell types (e.g., HL-60, Jurkat, CCRF-CEM, and Raji). Coadministration of PD184352 and UCN-01 resulted in reduced binding of the cdc25C phosphatase to 14-3-3 proteins, enhanced dephosphorylation/activation of p34cdc2, and diminished phosphorylation of cAMP-responsive element binding protein. The ability of UCN-01, when combined with PD184352, to antagonize cdc25C/14-3-3 protein binding, promote dephosphorylation of p34cdc2, and potentiate apoptosis was mimicked by the ataxia telangiectasia mutation inhibitor caffeine. In contrast, cotreatment of cells with UCN-01 and PD184352 did not substantially increase c-Jun-NH2-terminal kinase activation nor did it alter expression of Bcl-2, Bcl-xL, Bax, or X-inhibitor of apoptosis. However, coexposure of U937 cells to UCN-01 and PD184352 induced a marked increase in p38 MAPK activation. Moreover, SB203580, which inhibits multiple kinases including p38 MAPK, partially antagonized cell death. Lastly, although UCN-01 + PD184352 did not induce p21CIP1, stable expression of a p21CIP1 antisense construct significantly increased susceptibility to this drug combination. Together, these findings indicate that exposure of leukemic cells to UCN-01 leads to activation of the MAPK cascade and that interruption of this process by MEK inhibition triggers perturbations in several signaling and cell cycle regulatory pathways that culminate in mitochondrial injury, caspase activation, and apoptosis. They also raise the possibility that disrupting multiple signaling pathways, e.g., by combining UCN-01 with MEK inhibitors, may represent a novel antileukemic strategy.

ST MEK inhibitor UCN01 leukemia therapy signal transduction

IT Proteins, specific or class

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(14-3-3; pharmacol. inhibitors of MAPK kinase/MAPK cascade interact synergistically with UCN-01 to induce mitochondrial dysfunction and apoptosis in human leukemia cells via perturbations in several signaling and cell cycle regulatory pathways)

IT Proteins, specific or class

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(Bax; pharmacol. inhibitors of MAPK kinase/MAPK cascade interact synergistically with UCN-01 to induce mitochondrial dysfunction and apoptosis in human leukemia cells via perturbations in several signaling and cell cycle regulatory pathways)

IT Proteins, specific or class

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(Bcl-xL; pharmacol. inhibitors of MAPK kinase/MAPK cascade interact synergistically with UCN-01 to induce mitochondrial dysfunction and apoptosis in human leukemia cells via perturbations in several signaling and cell cycle regulatory pathways)

IT Transcription factors

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)  
 (CREB (cAMP-responsive element-binding); pharmacol. inhibitors of MAPK kinase/MAPK cascade interact synergistically with UCN-01 to induce mitochondrial dysfunction and apoptosis in human leukemia cells via perturbations in several signaling and cell cycle regulatory pathways)

IT Proteins, specific or class  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (XIAP; pharmacol. inhibitors of MAPK kinase/MAPK cascade interact synergistically with UCN-01 to induce mitochondrial dysfunction and apoptosis in human leukemia cells via perturbations in several signaling and cell cycle regulatory pathways)

IT Proteins, specific or class  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (bcl-2; pharmacol. inhibitors of MAPK kinase/MAPK cascade interact synergistically with UCN-01 to induce mitochondrial dysfunction and apoptosis in human leukemia cells via perturbations in several signaling and cell cycle regulatory pathways)

IT Antitumor agents  
 (leukemia; pharmacol. inhibitors of MAPK kinase/MAPK cascade interact synergistically with UCN-01 to induce mitochondrial dysfunction and apoptosis in human leukemia cells via perturbations in several signaling and cell cycle regulatory pathways)

IT Apoptosis  
 Cell cycle  
 Dephosphorylation, biological  
 Mitochondria  
 Signal transduction, biological  
 (pharmacol. inhibitors of MAPK kinase/MAPK cascade interact synergistically with UCN-01 to induce mitochondrial dysfunction and apoptosis in human leukemia cells via perturbations in several signaling and cell cycle regulatory pathways)

IT Phosphorylation, biological  
 (protein; pharmacol. inhibitors of MAPK kinase/MAPK cascade interact synergistically with UCN-01 to induce mitochondrial dysfunction and apoptosis in human leukemia cells via perturbations in several signaling and cell cycle regulatory pathways)

IT Drug interactions  
 (synergistic; pharmacol. inhibitors of MAPK kinase/MAPK cascade interact synergistically with UCN-01 to induce mitochondrial dysfunction and apoptosis in human leukemia cells via perturbations in several signaling and cell cycle regulatory pathways)

IT 186322-81-6, Caspase  
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (pharmacol. inhibitors of MAPK kinase/MAPK cascade interact synergistically with UCN-01 to induce mitochondrial dysfunction and apoptosis in human leukemia cells via perturbations in several signaling and cell cycle regulatory pathways)

IT 109511-58-2, U0126 112953-11-4, UCN-01 152121-47-6, SB203580 167869-21-8, PD98059 212631-79-3, PD184352  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)  
 (pharmacol. inhibitors of MAPK kinase/MAPK cascade interact synergistically with UCN-01 to induce mitochondrial dysfunction and apoptosis in human leukemia cells via perturbations in several signaling and cell cycle regulatory pathways)

IT 137632-07-6, p44 Mitogen-activated protein kinase 137632-08-7, p42 Mitogen-activated protein kinase 140208-22-6, Cdc25C phosphatase 143375-65-9 155215-87-5 165245-96-5, p38 Mitogen-activated protein

kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(pharmacol. inhibitors of MAPK kinase/MAPK cascade interact synergistically with UCN-01 to induce mitochondrial dysfunction and apoptosis in human leukemia cells via perturbations in several signaling and cell cycle regulatory pathways)

IT 142243-02-5, Mitogen-activated protein kinase 142805-58-1, Mitogen-activated protein kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(pharmacol. inhibitors of MAPK kinase/MAPK cascade interact synergistically with UCN-01 to induce mitochondrial dysfunction and apoptosis in human leukemia cells via perturbations in several signaling and cell cycle regulatory pathways)

RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD  
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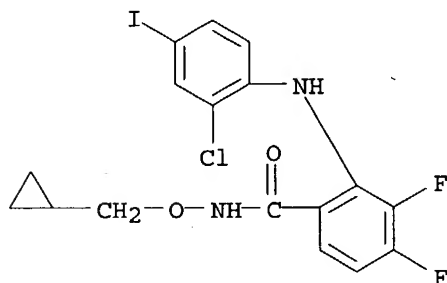
IT 212631-79-3, PD184352

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pharmacol. inhibitors of MAPK kinase/MAPK cascade interact synergistically with UCN-01 to induce mitochondrial dysfunction and apoptosis in human leukemia cells via perturbations in several signaling and cell cycle regulatory pathways)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 8 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:362914 HCAPLUS

DN 135:251181

ED Entered STN: 20 May 2001

TI Pharmacologic inhibitors of MKK1 and MKK2

AU Ahn, Natalie G.; Nahreini, Theresa Stines; Tolwinski, Nicholas S.; Resing, Katheryn A.

CS USA

SO Methods in Enzymology (2001), 332(Regulators and Effectors of Small GTPases, Part F), 417-431  
CODEN: MENZAU; ISSN: 0076-6879

PB Academic Press

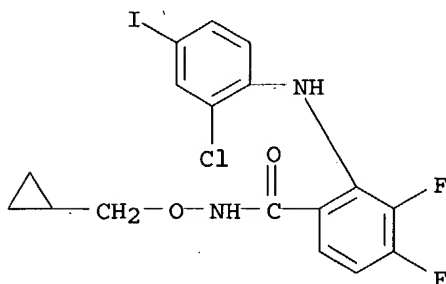
DT Journal; General Review

LA English

CC 1-0 (Pharmacology)

AB A review, with 26 refs., covers the inhibitor effects on activation and activity of mitogen-activated protein (MAP) kinase kinases 1 (MKK1) in vitro; inhibitor effects in intact cells; drug effects on extracellular signal-regulated kinases activation; mechanism of inhibitor action; and evaluation of inhibitor specificity. (c) 2001 Academic Press.

ST review MKK1 MKK2 inhibitor  
IT 109511-58-2, U0126 167869-21-8, PD 98059 212631-79-3, PD 184352  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(pharmacol. inhibitors of MKK1 and MKK2)  
IT 142243-02-5  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(pharmacol. inhibitors of MKK1 and MKK2)  
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD  
RE  
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IT 212631-79-3, PD 184352  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
(pharmacol. inhibitors of MKK1 and MKK2)  
RN 212631-79-3 HCAPLUS  
CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



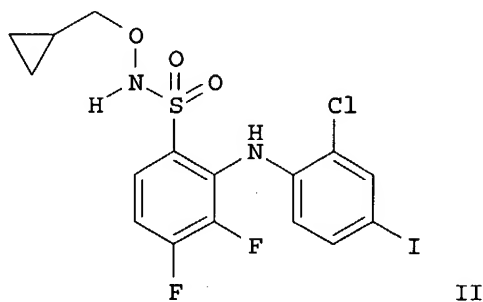
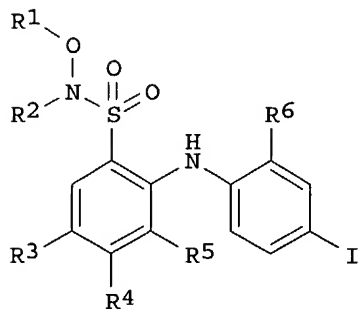
TI Preparation of (phenylamino)benzenesulfonamides and  
(phenylamino)benzamides as MEK inhibitors for the treatment of chronic  
pain  
IN Bridges, Alexander James; Booth, Richard John; Tecle, Haile; Scaggs,  
Yvonne; Kaufman, Michael; Barrett, Stephen Douglas; Dixon, Alistair; Lee,  
Kevin; Pinnock, Robert Denham  
PA Warner-Lambert Company, USA  
SO PCT Int. Appl., 158 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
IC ICM A61K031-00  
CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)  
Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001005393	A2	20010125	WO 2000-US18348	20000705 <--
	WO 2001005393	A3	20010510		
	W:		AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM		
	RW:		GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG		
	EP 1202724	A2	20020508	EP 2000-945140	20000705 <--
	EP 1202724	B1	20031001		
	R:		AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL		
	TR 200200205	T2	20020621	TR 2002-20020020520000705	<--
	AT 250932	E	20031015	AT 2000-945140	20000705 <--
	PT 1202724	T	20040227	PT 2000-945140	20000705 <--
	ZA 2001009909	A	20030228	ZA 2001-9909	20011130 <--
PRAI	US 1999-144280P	P	19990716	<--	
	US 1999-144320P	P	19990716	<--	
	US 1999-144419P	P	19990716	<--	
	US 1999-144655P	P	19990716	<--	
	US 1999-144658P	P	19990716	<--	
	US 1999-144659P	P	19990716	<--	
	WO 2000-US18348	W	20000705	<--	

OS MARPAT 134:131318

GI



AB The title compds. (I) [wherein R1 = H, (phenyl)alkyl, (phenyl)alkenyl, (phenyl)alkynyl, cycloalkyl, Ph, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, alkoxylalkyl, phenoxyalkyl, (un)substituted

aminoalkyl, piperidinoalkyl, morpholinoalkyl, or alkylpiperazinoalkyl; R2 = H, (cyclo)alkyl, Ph, heterocyclyl, or cycloalkylmethyl; R3 and R4 = independently H, F, NO2, Br, or Cl; R5 = H or F; R6 = H, F, Cl, or Me] were prepared for the treatment of chronic pain. For example, 2,3,4-trifluorobenzenesulfonyl chloride was amidated O-cyclopropylmethylhydroxylamine•HCl in CH2Cl2 using diisopropylethylamine (68%). Coupling with 2-chloro-4-iodoaniline in THF in the presence of Li bis(trimethylsilyl)amide afforded PD 297447 (II) in 73% yield. The APK IC50 for PD 297447 was 0.965  $\mu$ M. Intrathecally administered II (30 $\mu$ g) showed no significant effect on allodynia in the CCI model of neuropathic pain in rats, perhaps due to low affinity or solubility of the compound. However, related MEK inhibitors with higher affinities exerted an antiallodynic effect in CCI-induced neuropathic rats.

- ST phenylamino benzamide benzenesulfonamide prepn mek inhibitor; sulfamoyl benzamide prepn analgesic; benzamide phenylamino sulfamoyl prepn chronic pain treatment
- IT Pain  
Skin, disease  
(allodynia, treatment; preparation of (phenylamino)benzenesulfonamides and (phenylamino)benzamides as MEK inhibitors for treatment of chronic pain)
- IT Vitamins  
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)  
(avitaminosis, treatment of pain associated with; preparation of (phenylamino)benzenesulfonamides and (phenylamino)benzamides as MEK inhibitors for treatment of chronic pain)
- IT Kidney, disease  
(failure, treatment of pain associated with; preparation of (phenylamino)benzenesulfonamides and (phenylamino)benzamides as MEK inhibitors for treatment of chronic pain)
- IT Analgesics  
(preparation of (phenylamino)benzenesulfonamides and (phenylamino)benzamides as MEK inhibitors for treatment of chronic pain)
- IT Pain  
(treatment of idiopathic and post-operative; preparation of (phenylamino)benzenesulfonamides and (phenylamino)benzamides as MEK inhibitors for treatment of chronic pain)
- IT Alcoholism  
Arthritis  
Hypothyroidism  
Inflammation  
(treatment of pain associated with; preparation of (phenylamino)benzenesulfonamides and (phenylamino)benzamides as MEK inhibitors for treatment of chronic pain)
- IT 3463-30-7P, 1-(4-Nitrophenyl)-1H-pyrazole 4533-42-0P, 1-(4-Nitrophenyl)-1H-pyrrole 13788-94-8P, 3,5-Dimethyl-1-(4-nitrophenyl)-1H-pyrazole 17635-45-9P, 4-1H-Pyrazol-1-ylphenylamine 52708-32-4P, 4-(3,5-Dimethyl-1H-pyrazol-1-yl)benzenamine 52768-17-9P, 4-Pyrrol-1-ylphenylamine 197520-71-1P, 5-Nitro-2,3,4-trifluorobenzoic acid 283602-30-2P, 4-Fluoro-2-(4-methanesulfanyphenylamino)benzoic acid 283602-31-3P, 4-Fluoro-2-(4-methanesulfinylphenylamino)benzoic acid 283602-32-4P, 4-Fluoro-2-(4-methanesulfonylphenylamino)benzoic acid 283602-33-5P, 2-Methyl-4-trimethylsilanylethynylaniline 283602-34-6P, 283602-35-7P, 4-Fluoro-2-(4-pyrrol-1-ylphenylamino)benzoic acid 283602-36-8P, 4-Fluoro-2-(4-pyrazol-1-ylphenylamino)benzoic acid 283602-37-9P, 2-[4-(3,5-Dimethylpyrazol-1-yl)phenylamino]-4-fluorobenzoic acid 283602-38-0P, N-Cyclopropylmethoxy-2,3,4-trifluorobenzenesulfonamide 285127-07-3P, 5-Dimethylsulfamoyl-2,3,4-trifluorobenzoic acid 285127-08-4P, 5-Dimethylsulfamoyl-2,3,4-trifluorobenzoic acid methyl ester 285127-09-5P, 1-Bis(4-methoxybenzyl)sulfamoyl-2,3,4-trifluorobenzene 285127-10-8P,

5-Bis(4-methoxybenzyl)sulfamoyl-2,3,4-trifluorobenzoic acid  
 285127-11-9P, 5-Bis(4-methoxybenzyl)sulfamoyl-2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide  
 285127-13-1P, 2-(2-Chloro-4-iodophenylamino)-3,4-difluoro-5-dimethylsulfamoylbenzoic acid 285127-14-2P, 3,4-Difluoro-5-dimethylsulfamoyl-2-(4-iodo-2-methylphenylamino)benzoic acid  
 321166-95-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of (phenylamino)benzenesulfonamides and (phenylamino)benzamides as MEK inhibitors for treatment of chronic pain)

IT 283602-00-6P, 4-Fluoro-2-(2-methyl-4-ethynylphenylamino)benzoic acid  
 285125-84-0P, 2-(2-Chloro-4-iodophenylamino)-5-dimethylsulfamoyl-3,4-difluorobenzoic acid methyl ester 285126-98-9P, 5-Bis(4-methoxybenzyl)sulfamoyl-2-(2-chloro-4-iodophenylamino)-3,4-difluorobenzoic acid

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of (phenylamino)benzenesulfonamides and (phenylamino)benzamides as MEK inhibitors for treatment of chronic pain)

IT 219796-67-5P, 2,4-Bis(2-chloro-4-iodophenylamino)-3-fluoro-5-nitrobenzoic acid 283601-26-3P, 4-Fluoro-2-(2-methyl-4-methylsulfanylphenylamino)benzoic acid 283601-27-4P, 5-Bromo-3,4-difluoro-2-(2-methyl-4-methylsulfanylphenylamino)benzoic acid 283601-28-5P, 3,4-Difluoro-2-(4-methanesulfinyl-2-methylphenylamino)benzoic acid 283601-29-6P, 2-(4-Methanesulfinyl-2-methylphenylamino)-4-nitrobenzoic acid 283601-30-9P, 3,4,5-Trifluoro-2-(4-methanesulfonyl-2-methylphenylamino)benzoic acid 283601-31-0P, 3,4-Difluoro-2-(2-methyl-4-methylsulfanylphenylamino)benzoic acid 283601-32-1P, 2-(2-Methyl-4-methylsulfanylphenylamino)-4-nitrobenzoic acid 283601-33-2P, 3,4,5-Trifluoro-2-(4-methanesulfinyl-2-methylphenylamino)benzoic acid 283601-34-3P, 4-Fluoro-2-(4-methanesulfinyl-2-methylphenylamino)benzoic acid 283601-35-4P, 5-Bromo-3,4-difluoro-2-(4-methanesulfonyl-2-methylphenylamino)benzoic acid 283601-37-6P, 5-Bromo-3,4-difluoro-2-(4-methanesulfinyl-2-methylphenylamino)benzoic acid 283601-38-7P, 3,4-Difluoro-2-(4-methanesulfonyl-2-methylphenylamino)benzoic acid 283601-39-8P, 2-(4-Methanesulfonyl-2-methylphenylamino)-4-nitrobenzoic acid 283601-40-1P, N-Cyclopropylmethoxy-4-fluoro-2-(2-methyl-4-methylsulfanylphenylamino)benzamide 283601-41-2P, 5-Bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(2-methyl-4-methylsulfanylphenylamino)benzamide 283601-42-3P, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfinyl-2-methylphenylamino)benzamide 283601-43-4P, N-Cyclopropylmethoxy-2-(4-methanesulfinyl-2-methylphenylamino)-4-nitrobenzamide 283601-44-5P, N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-methanesulfonyl-2-methylphenylamino)benzamide 283601-45-6P, N-Cyclopropylmethoxy-3,4-difluoro-2-(2-methyl-4-methylsulfanylphenylamino)benzamide 283601-46-7P, N-Cyclopropylmethoxy-2-(2-methyl-4-methylsulfanylphenylamino)-4-nitrobenzamide 283601-47-8P, N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-methanesulfinyl-2-methylphenylamino)benzamide 283601-48-9P, N-Cyclopropylmethoxy-4-fluoro-2-(4-methanesulfinyl-2-methylphenylamino)benzamide 283601-49-0P, 5-Bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfonyl-2-methylphenylamino)benzamide 283601-50-3P, N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(2-methyl-4-methylsulfanylphenylamino)benzamide 283601-51-4P, 5-Bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfinyl-2-methylphenylamino)benzamide 283601-52-5P, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-methanesulfonyl-2-methylphenylamino)benzamide 283601-53-6P, N-Cyclopropylmethoxy-2-(4-methanesulfonyl-2-methylphenylamino)-4-nitrobenzamide 283601-54-7P,

4-Fluoro-N-hydroxy-2-(2-methyl-4-methylsulfanyphenylamino)benzamide  
283601-55-8P, 5-Bromo-3,4-difluoro-N-hydroxy-2-(2-methyl-4-methylsulfanyphenylamino)benzamide 283601-56-9P, 3,4-Difluoro-N-hydroxy-2-(4-methanesulfinyl-2-methylphenylamino)benzamide 283601-57-0P, N-Hydroxy-2-(4-methanesulfinyl-2-methylphenylamino)-4-nitrobenzamide 283601-59-2P, 3,4,5-Trifluoro-N-hydroxy-2-(4-methanesulfonyl-2-methylphenylamino)benzamide 283601-60-5P, 3,4-Difluoro-N-hydroxy-2-(2-methyl-4-methylsulfanyphenylamino)benzamide 283601-61-6P, N-Hydroxy-2-(2-methyl-4-methylsulfanyphenylamino)-4-nitrobenzamide 283601-62-7P, 3,4,5-Trifluoro-N-hydroxy-2-(4-methanesulfinyl-2-methylphenylamino)benzamide 283601-63-8P, 4-Fluoro-N-hydroxy-2-(4-methanesulfinyl-2-methylphenylamino)benzamide 283601-64-9P, 5-Bromo-3,4-difluoro-N-hydroxy-2-(4-methanesulfonyl-2-methylphenylamino)benzamide 283601-65-0P, 3,4,5-Trifluoro-N-hydroxy-2-(2-methyl-4-methylsulfanyphenylamino)benzamide 283601-66-1P, 5-Bromo-3,4-difluoro-N-hydroxy-2-(4-methanesulfinyl-2-methylphenylamino)benzamide 283601-67-2P, 3,4-Difluoro-N-hydroxy-2-(4-methanesulfonyl-2-methylphenylamino)benzamide 283601-68-3P, N-Hydroxy-2-(4-methanesulfonyl-2-methylphenylamino)-4-nitrobenzamide 283601-69-4P, 3,4-Difluoro-2-(4-imidazol-1-yl-2-methylphenylamino)benzoic acid 283601-70-7P, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-imidazol-1-yl-2-methylphenylamino)benzamide 283601-71-8P, 3,4-Difluoro-N-hydroxy-2-(4-imidazol-1-yl-2-methylphenylamino)benzamide 283601-72-9P, 3,4,5-Trifluoro-2-(2-methyl-4-[1,2,5]thiadiazol-3-ylphenylamino)benzoic acid 283601-73-0P, N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(2-methyl-4-[1,2,5]thiadiazol-3-ylphenylamino)benzamide 283601-74-1P, 3,4,5-Trifluoro-N-hydroxy-2-(2-methyl-4-[1,2,5]thiadiazol-3-ylphenylamino)benzamide 283601-75-2P, 2-[4-(4-Chloro-[1,2,5]thiadiazol-3-yl)-2-methylphenylamino]-3,4,5-trifluorobenzoic acid 283601-76-3P, 2-[4-(4-Chloro-[1,2,5]thiadiazol-3-yl)-2-methylphenylamino]-N-cyclopropylmethoxy-3,4,5-trifluorobenzamide 283601-77-4P, 2-[4-(4-Chloro-[1,2,5]thiadiazol-3-yl)-2-methylphenylamino]-3,4,5-trifluoro-N-hydroxybenzamide 283601-78-5P, 2-[4-(4-(2-Dimethylaminoethoxy)-[1,2,5]thiadiazol-3-yl)-2-methylphenylamino]-3,4,5-trifluorobenzoic acid 283601-79-6P, N-Cyclopropylmethoxy-3,4,5-trifluoro-2-[2-methyl-4-[4-(2-piperidin-1-ylethoxy)-[1,2,5]thiadiazol-3-yl]phenylamino]benzamide 283601-80-9P, 3,4,5-Trifluoro-N-hydroxy-2-[2-methyl-4-[4-(2-morpholin-4-ylethoxy)-[1,2,5]thiadiazol-3-yl]phenylamino]benzamide 283601-81-0P, 5-Bromo-2-(2-chloro-4-methylsulfanyphenylamino)-3,4-difluorobenzoic acid 283601-82-1P, 2-(2-Chloro-4-methanesulfinylphenylamino)-3,4-difluorobenzoic acid 283601-83-2P, 2-(2-Chloro-4-methanesulfonylphenylamino)-3,4,5-trifluorobenzoic acid 283601-84-3P 283601-85-4P, 5-Bromo-2-(2-chloro-4-methanesulfonylphenylamino)-3,4-difluorobenzoic acid 283601-86-5P, 2-(2-Chloro-4-methanesulfonylphenylamino)-3,4-difluorobenzoic acid 283601-87-6P, 5-Bromo-2-(2-chloro-4-methylsulfanyphenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide 283601-88-7P, 2-(2-Chloro-4-methanesulfinylphenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide 283601-89-8P, 2-(2-Chloro-4-methanesulfonylphenylamino)-N-cyclopropylmethoxy-3,4,5-trifluorobenzamide 283601-90-1P, 2-(2-Chloro-4-methylsulfanyphenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide 283601-91-2P, 2-(2-Chloro-4-methanesulfinylphenylamino)-N-cyclopropylmethoxy-3,4,5-trifluorobenzamide 283601-92-3P, 5-Bromo-2-(2-chloro-4-methanesulfonylphenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide 283601-93-4P, 2-(2-Chloro-4-methylsulfanyphenylamino)-N-cyclopropylmethoxy-3,4,5-trifluorobenzamide 283601-94-5P, 2-(2-Chloro-4-methanesulfonylphenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide 283601-95-6P 283601-96-7P, 2-(2-Chloro-4-[1,2,5]thiadiazol-3-ylphenylamino)-N-cyclopropylmethoxy-3,4,5-trifluorobenzamide 283601-97-8P 283601-98-9P 283601-99-0P 283602-01-7P, 5-Bromo-2-(4-ethynyl-2-methylphenylamino)-3,4-difluorobenzoic acid 283602-02-8P, N-Cyclopropylmethoxy-2-(4-ethynyl-2-

methylphenylamino)-3,4-difluorobenzamide 283602-03-9P,  
N-Cyclopropylmethoxy-2-(4-ethynyl-2-methylphenylamino)-4-nitrobenzamide  
283602-04-0P, 2-(4-Ethynyl-2-methylphenylamino)-3,4,5-trifluoro-N-  
hydroxybenzamide 283602-05-1P, 2-(4-Ethynyl-2-methylphenylamino)-3,4-  
difluorobenzoic acid 283602-06-2P, 2-(4-Ethynyl-2-methylphenylamino)-4-  
nitrobenzoic acid 283602-07-3P, N-Cyclopropylmethoxy-2-(4-ethynyl-2-  
methylphenylamino)-3,4,5-trifluorobenzamide 283602-08-4P,  
5-Bromo-2-(4-ethynyl-2-methylphenylamino)-3,4-difluoro-N-hydroxybenzamide  
283602-09-5P, 2-(4-Ethynyl-2-methylphenylamino)-3,4,5-trifluorobenzoic  
acid 283602-10-8P, N-Cyclopropylmethoxy-2-(4-ethynyl-2-  
methylphenylamino)-4-fluorobenzamide 283602-11-9P, 5-Bromo-N-  
cyclopropylmethoxy-2-(4-ethynyl-2-methylphenylamino)-3,4-difluorobenzamide  
283602-12-0P, 2-(4-Ethynyl-2-methylphenylamino)-3,4-difluoro-N-  
hydroxybenzamide 283602-13-1P, 2-(4-Ethynyl-2-methylphenylamino)-N-  
hydroxy-4-nitrobenzamide 283602-14-2P, 2-(2-Chloro-4-ethynylphenylamino)-  
4-fluorobenzoic acid 283602-15-3P, 5-Bromo-2-(2-chloro-4-  
ethynylphenylamino)-3,4-difluorobenzoic acid 283602-16-4P,  
2-(2-Chloro-4-ethynylphenylamino)-N-cyclopropylmethoxy-3,4-  
difluorobenzamide 283602-17-5P, 2-(2-Chloro-4-ethynylphenylamino)-N-  
cyclopropylmethoxy-4-nitrobenzamide 283602-18-6P, 2-(2-Chloro-4-  
ethynylphenylamino)-N-hydroxy-3,4,5-trifluorobenzamide 283602-19-7P,  
2-(2-Chloro-4-ethynylphenylamino)-3,4-difluorobenzoic acid 283602-20-0P,  
2-(4-Ethynyl-2-chlorophenylamino)-4-nitrobenzoic acid 283602-21-1P,  
2-(2-Chloro-4-ethynylphenylamino)-N-Cyclopropylmethoxy-3,4,5-  
trifluorobenzamide 283602-22-2P, 2-(2-Chloro-4-  
methanesulfinylphenylamino)-4-fluoro-N-hydroxybenzamide 283602-23-3P,  
5-Bromo-2-(4-ethynyl-2-chlorophenylamino)-3,4-difluoro-N-hydroxybenzamide  
283602-24-4P, 2-(2-Chloro-4-ethynylphenylamino)-3,4,5-trifluorobenzoic  
acid 283602-25-5P, 2-(2-Chloro-4-ethynylphenylamino)-N-  
cyclopropylmethoxy-4-fluorobenzamide 283602-26-6P, 5-Bromo-2-(2-chloro-4-  
ethynylphenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide  
283602-27-7P, 2-(4-Ethynyl-2-chlorophenylamino)-3,4-difluoro-N-  
hydroxybenzamide 283602-28-8P, 2-(4-Ethynyl-2-chlorophenylamino)-N-  
hydroxy-4-nitrobenzamide 283602-29-9P, 2-(2-Chloro-4-imidazol-1-  
ylphenylamino)-3,4-Difluorobenzoic acid 283602-39-1P,  
2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-  
difluorobenzenesulfonamide 284018-87-7P, 2-(2-Chloro-4-iodophenylamino)-  
3-fluoro-5-nitro-4-phenylaminobenzoic acid 284018-90-2P,  
2-(2-Chloro-4-iodophenylamino)-3-fluoro-5-nitro-4-(4-  
sulfamoylphenylamino)benzoic acid 284018-93-5P, 2-(2-Chloro-4-  
iodophenylamino)-3-fluoro-5-nitro-4-phenoxybenzoic acid 284018-96-8P,  
2-(2-Chloro-4-iodophenylamino)-3-fluoro-5-nitro-4-phenylsulfanylbenzoic  
acid 284018-99-1P 284019-03-0P, 2-[(2-Chloro-4-iodophenyl)amino]-4-[[4-  
[(dimethylamino)carbonyl]phenyl]amino]-3-fluoro-N-hydroxy-5-nitrobenzamide  
284019-06-3P, 2-[(2-Chloro-4-iodophenyl)amino]-3-fluoro-N-hydroxy-4-[[4-  
[(2-hydroxyethyl)amino]carbonyl]phenyl]amino]-5-nitrobenzamide  
284019-08-5P, 2-(2-Chloro-4-iodophenylamino)-3,5-difluoro-4-  
phenylaminobenzoic acid 284020-52-6P, 4-Fluoro-2-(4-iodo-2-  
methylphenylamino)benzenesulfonic acid 284020-53-7P,  
4-Fluoro-N-hydroxy-2-(4-iodo-2-methylphenylamino)benzenesulfonamide  
284020-54-8P, N-Cyclopropylmethoxy-4-fluoro-2-(4-iodo-2-  
methylphenylamino)benzenesulfonamide 284020-55-9P, 3,4-Difluoro-2-(4-  
iodo-2-methylphenylamino)benzenesulfonic acid 284020-56-0P,  
3,4-Difluoro-N-hydroxy-2-(4-iodo-2-methylphenylamino)benzenesulfonamide  
284020-57-1P, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-  
methylphenylamino)benzenesulfonamide 284020-58-2P, 3,4,5-Trifluoro-2-(4-  
iodo-2-methylphenylamino)benzenesulfonic acid 284020-59-3P,  
3,4,5-Trifluoro-N-hydroxy-2-(4-iodo-2-methylphenylamino)benzenesulfonamide  
284020-60-6P, N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-  
methylphenylamino)benzenesulfonamide 284020-61-7P, 5-Bromo-3,4-difluoro-  
2-(4-iodo-2-methylphenylamino)benzenesulfonic acid 284020-62-8P,  
5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methylphenylamino)benzenesulfon-  
amide 284020-63-9P, 5-Bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-

2-methylphenylamino)benzenesulfonamide 284020-64-0P,  
2-(4-Iodo-2-methylphenylamino)-4-nitrobenzenesulfonic acid 284020-65-1P,  
N-Hydroxy-2-(4-iodo-2-methylphenylamino)-4-nitrobenzenesulfonamide  
284020-66-2P, N-Cyclopropylmethoxy-2-(4-iodo-2-methylphenylamino)-4-  
nitrobenzenesulfonamide 284020-67-3P, 2-(2-Chloro-4-iodophenylamino)-4-  
fluorobenzenesulfonic acid 284020-68-4P, 2-(2-Chloro-4-iodophenylamino)-  
4-fluoro-N-hydroxybenzenesulfonamide 284020-69-5P, 2-(2-Chloro-4-  
iodophenylamino)-N-cyclopropylmethoxy-4-fluorobenzenesulfonamide  
284020-70-8P, 2-(2-Chloro-4-iodophenylamino)-3,4-difluorobenzenesulfonic  
acid 284020-71-9P, 2-(2-Chloro-4-iodophenylamino)-3,4-difluoro-N-  
hydroxybenzenesulfonamide 284020-72-0P, 2-(2-Chloro-4-iodophenylamino)-  
3,4,5-trifluorobenzenesulfonic acid 284020-73-1P, 2-(2-Chloro-4-  
iodophenylamino)-3,4,5-trifluoro-N-hydroxybenzenesulfonamide  
284020-74-2P, 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4,5-  
trifluorobenzenesulfonamide 284020-75-3P, 5-Bromo-2-(2-chloro-4-  
iodophenylamino)-3,4-difluorobenzenesulfonic acid 284020-76-4P,  
5-Bromo-2-(2-chloro-4-iodophenylamino)-3,4-difluoro-N-  
hydroxybenzenesulfonamide 284020-77-5P, 5-Bromo-2-(2-chloro-4-  
iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzenesulfonamide  
284020-78-6P, 2-(2-Chloro-4-iodophenylamino)-4-nitrobenzenesulfonic acid  
284020-79-7P, 2-(2-Chloro-4-iodophenylamino)-N-hydroxy-4-  
nitrobenzenesulfonamide 284020-80-0P, 2-(2-Chloro-4-iodophenylamino)-N-  
cyclopropylmethoxy-4-nitrobenzenesulfonamide 285125-85-1P,  
2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-  
sulfamoylbenzamide 285125-86-2P, 2-(2-Chloro-4-iodophenylamino)-3,4-  
difluoro-N-hydroxy-5-sulfamoylbenzamide 285125-87-3P,  
2-(2-Chloro-4-iodophenylamino)-3,4-difluoro-5-sulfamoylbenzoic acid  
285125-88-4P, 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-  
difluoro-5-dimethylsulfamoylbenzamide 285125-89-5P, N-Cyclopropylmethoxy-  
3,4-difluoro-5-dimethylsulfamoyl-2-(4-iodo-2-methylphenylamino)benzamide  
285125-91-9P, 2-(2-Chloro-4-iodophenylamino)-4-sulfamoylbenzoic acid  
285125-92-0P, 2-(2-Chloro-4-iodophenylamino)-N-hydroxy-4-  
sulfamoylbenzamide 285125-93-1P, 2-(2-Chloro-4-iodophenylamino)-N-  
cyclopropylmethoxy-4-sulfamoylbenzamide 285125-94-2P,  
2-(2-Chloro-4-iodophenylamino)-4-(2-morpholin-4-ylethylsulfamoyl)benzoic  
acid 285125-95-3P, 2-(2-Chloro-4-iodophenylamino)-N-hydroxy-4-(2-  
morpholin-4-ylethylsulfamoyl)benzamide 285125-96-4P,  
2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-4-(2-morpholin-4-  
ylethylsulfamoyl)benzamide 285125-97-5P, 2-(2-Chloro-4-iodophenylamino)-  
3,4-difluoro-5-(2-morpholin-4-ylethylsulfamoyl)benzoic acid  
285125-98-6P, 2-(2-Chloro-4-iodophenylamino)-3,4-difluoro-N-hydroxy-5-(2-  
morpholin-4-ylethylsulfamoyl)benzamide 285125-99-7P,  
2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-(2-  
morpholin-4-ylethylsulfamoyl)benzamide 285126-00-3P,  
5-(Bispyridin-3-ylmethylsulfamoyl)-3,4-difluoro-2-(4-  
iodophenylamino)benzoic acid 285126-01-4P, 5-(Bispyridin-3-  
ylmethylsulfamoyl)-N-cyclopropylmethoxy-3,4-difluoro-2-(4-  
iodophenylamino)benzamide 285126-02-5P 285126-03-6P,  
N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodophenylamino)-5-[(pyridin-3-  
ylmethyl)sulfamoyl]benzamide 285126-04-7P, N-Cyclopropylmethoxy-5-[(3-  
diethylaminopropyl)pyridin-3-ylmethylsulfamoyl]-3,4-difluoro-2-(4-  
iodophenylamino)benzamide 285126-05-8P, N-Cyclopropylmethoxy-3,4-  
difluoro-5-[(3-hydroxypropyl)pyridin-3-ylmethylsulfamoyl]-2-(4-  
iodophenylamino)benzamide 285126-06-9P 285126-07-0P,  
N-Cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxyethyl)pyridin-3-  
ylmethylsulfamoyl]-2-(4-iodophenylamino)benzamide 285126-08-1P,  
5-(Bispyridin-2-ylmethylsulfamoyl)-3,4-difluoro-2-(4-  
iodophenylamino)benzoic acid 285126-09-2P, 5-(Bispyridin-2-  
ylmethylsulfamoyl)-N-cyclopropylmethoxy-3,4-difluoro-2-(4-  
iodophenylamino)benzamide 285126-10-5P, N-Cyclopropylmethoxy-3,4-  
difluoro-2-(4-iodophenylamino)-5-(methylpyridin-2-  
ylmethylsulfamoyl)benzamide 285126-11-6P, N-Cyclopropylmethoxy-3,4-  
difluoro-2-(4-iodophenylamino)-5-[(pyridin-2-ylmethyl)sulfamoyl]benzamide

285126-12-7P, 5-(Bispyridin-3-ylmethylsulfamoyl)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 285126-13-8P, 5-(Bispyridin-3-ylmethylsulfamoyl)-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 285126-14-9P 285126-15-0P, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-5-[(pyridin-3-ylmethyl)sulfamoyl]benzamide 285126-16-1P, N-Cyclopropylmethoxy-5-[(3-diethylaminopropyl)pyridin-3-ylmethylsulfamoyl]-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 285126-17-2P, N-Cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxypropyl)pyridin-3-ylmethylsulfamoyl]-2-(4-iodo-2-methylphenylamino)benzamide 285126-18-3P 285126-19-4P, N-Cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxyethyl)pyridin-3-ylmethylsulfamoyl]-2-(4-iodo-2-methylphenylamino)benzamide 285126-20-7P, 5-(Bispyridin-2-ylmethylsulfamoyl)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 285126-21-8P, 5-(Bispyridin-2-ylmethylsulfamoyl)-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 285126-22-9P 285126-23-0P, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-5-[(pyridin-2-ylmethyl)sulfamoyl]benzamide 285126-24-1P, 5-(Bispyridin-3-ylmethylsulfamoyl)-2-(2-chloro-4-iodophenylamino)-3,4-difluorobenzoic acid 285126-25-2P, 5-(Bispyridin-3-ylmethylsulfamoyl)-2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide 285126-26-3P 285126-27-4P, 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(pyridin-3-ylmethyl)sulfamoyl]benzamide 285126-28-5P, 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-5-[(3-diethylaminopropyl)pyridin-3-ylmethylsulfamoyl]-3,4-difluorobenzamide 285126-29-6P, 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxypropyl)pyridin-3-ylmethylsulfamoyl]benzamide 285126-30-9P 285126-31-0P, 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxyethyl)pyridin-3-ylmethylsulfamoyl]benzamide 285126-32-1P, 5-(Bispyridin-2-ylmethylsulfamoyl)-2-(2-chloro-4-iodophenylamino)-3,4-difluorobenzoic acid 285126-33-2P, 5-(Bispyridin-2-ylmethylsulfamoyl)-2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide 285126-34-3P 285126-35-4P, 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(pyridin-2-ylmethyl)sulfamoyl]benzamide 285126-36-5P, N-Cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxypropyl)pyridin-2-ylmethylsulfamoyl]-2-(4-iodophenylamino)benzamide 285126-37-6P, N-Cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxyethyl)pyridin-2-ylmethylsulfamoyl]-2-(4-iodophenylamino)benzamide 285126-38-7P, 5-(Benzylpyridin-2-ylmethylsulfamoyl)-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodophenylamino)benzamide 285126-39-8P, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodophenylamino)-5-[(pyridin-4-ylmethyl)sulfamoyl]benzamide 285126-40-1P 285126-41-2P 285126-42-3P, N-Cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxypropyl)pyridin-4-ylmethylsulfamoyl]-2-(4-iodophenylamino)benzamide 285126-43-4P, N-Cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxyethyl)pyridin-4-ylmethylsulfamoyl]-2-(4-iodophenylamino)benzamide 285126-44-5P 285126-45-6P, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodophenylamino)-5-phenylsulfamoylbenzamide 285126-46-7P, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodophenylamino)-5-(pyridin-3-ylsulfamoyl)benzamide 285126-47-8P, N-Cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxypropyl)pyridin-2-ylmethylsulfamoyl]-2-(4-iodo-2-methylphenylamino)benzamide 285126-48-9P, N-Cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxyethyl)pyridin-2-ylmethylsulfamoyl]-2-(4-iodo-2-methylphenylamino)benzamide 285126-49-0P, 5-(Benzylpyridin-2-ylmethylsulfamoyl)-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 285126-50-3P, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-5-[(pyridin-4-ylmethyl)sulfamoyl]benzamide 285126-51-4P 285126-52-5P 285126-53-6P, N-Cyclopropylmethoxy-3,4-difluoro-5-[(3-hydroxypropyl)pyridin-4-ylmethylsulfamoyl]-2-(4-iodo-2-methylphenylamino)benzamide 285126-54-7P, N-Cyclopropylmethoxy-3,4-difluoro-5-[(2-hydroxyethyl)pyridin-4-ylmethylsulfamoyl]-2-(4-iodo-2-methylphenylamino)benzamide 285126-55-8P 285126-56-9P, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-

methylphenylamino)-5-phenylsulfamoylbenzamide 285126-57-0P,  
 N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-5-  
 (pyridin-3-ylsulfamoyl)benzamide 285126-58-1P  
 , 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(3-  
 hydroxypropyl)pyridin-2-ylmethylsulfamoyl]benzamide 285126-59-2P,  
 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(2-  
 hydroxyethyl)pyridin-2-ylmethylsulfamoyl]benzamide 285126-60-5P,  
 5-(Benzylpyridin-2-ylmethylsulfamoyl)-2-(2-chloro-4-iodophenylamino)-N-  
 cyclopropylmethoxy-3,4-difluorobenzamide 285126-61-6P,  
 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-  
 [(pyridin-4-ylmethyl)sulfamoyl]benzamide 285126-62-7P,  
 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-5-(ethylpyridin-4-  
 ylmethylsulfamoyl)-3,4-difluorobenzamide 285126-63-8P,  
 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-  
 (methylpyridin-4-ylmethylsulfamoyl)benzamide 285126-64-9P,  
 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(3-  
 hydroxypropyl)pyridin-4-ylmethylsulfamoyl]benzamide 285126-65-0P,  
 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-[(2-  
 hydroxyethyl)pyridin-4-ylmethylsulfamoyl]benzamide 285126-66-1P,  
 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-  
 (methylphenylsulfamoyl)benzamide 285126-67-2P, 2-(2-Chloro-4-  
 iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-  
 phenylsulfamoylbenzamide 285126-68-3P, 2-(2-Chloro-4-iodophenylamino)-N-  
 cyclopropylmethoxy-3,4-difluoro-5-(pyridin-3-ylsulfamoyl)benzamide  
 285126-99-0P, N-Allyloxy-2-(2-chloro-4-iodophenylamino)-3,4-difluoro-5-(4-  
 methylpiperazinesulfonyl)benzamide 285127-00-6P, N-Allyloxy-2-(2-chloro-  
 4-iodophenylamino)-3,4-difluoro-5-(methylphenylsulfamoyl)benzamide  
 285127-01-7P, 5-(Allylmethylsulfamoyl)-N-allyloxy-2-(2-chloro-4-  
 iodophenylamino)-3,4-difluorobenzamide 285127-02-8P,  
 1-[5-Allyloxycarbamoyl-4-(2-chloro-4-iodophenylamino)-2,3-  
 difluorobenzenesulfonyl]piperidine-3-carboxylic acid amide 285127-03-9P,  
 N-Allyloxy-2-(2-chloro-4-iodophenylamino)-5-[(3-  
 dimethylaminopropyl)methylsulfamoyl]-3,4-difluorobenzamide 285127-04-0P,  
 N-Allyloxy-2-(2-chloro-4-iodophenylamino)-3,4-difluoro-5-(4-pyridin-2-  
 ylpiperazine-1-sulfonyl)benzamide 313676-66-3P, 2-(3',5'-  
 Dichlorobiphenyl-4-ylamino)benzoic acid 321167-78-6P,  
 2-(2-Chloro-4-iodophenylamino)-3-fluoro-5-nitro-4-(3-  
 sulfamoylphenylamino)benzoic acid 321167-81-1P, 2-(2-Chloro-4-  
 iodophenylamino)-3-fluoro-5-nitro-4-(2-sulfamoylphenylamino)benzoic acid  
 321168-04-1P, 3,4,5-Trifluoro-2-(2-methyl-4-methylsulfanyphenylamino)benz  
 oic acid 321171-65-7P, N-Cyclopropylmethoxy-2-(4-iodophenylamino)-4-  
 phenylsulfamoylbenzamide

RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);  
 BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of (phenylamino)benzenesulfonamides and (phenylamino)benzamides  
 as MEK inhibitors for treatment of chronic pain)

IT 321171-68-0P, N-Cyclopropylmethoxy-2-(4-iodophenylamino)-4-(pyridin-3-  
 ylsulfamoyl)benzamide 321171-71-5P, N-Cyclopropylmethoxy-2-(4-  
 iodophenylamino)-4-[(pyridin-3-ylmethyl)sulfamoyl]benzamide  
 321171-74-8P, 4-(Bispyridin-3-ylmethylsulfamoyl)-N-cyclopropylmethoxy-2-(4-  
 iodophenylamino)benzamide 321171-77-1P, N-Cyclopropylmethoxy-4-[(2-  
 hydroxyethyl)pyridin-4-ylmethylsulfamoyl]-2-(4-iodophenylamino)benzamide  
 321171-80-6P, N-Cyclopropylmethoxy-2-(4-iodophenylamino)-4-(methylpyridin-  
 3-ylmethylsulfamoyl)benzamide 321171-83-9P, N-Cyclopropylmethoxy-4-[(3-  
 diethylaminopropyl)pyridin-3-ylmethylsulfamoyl]-2-(4-  
 iodophenylamino)benzamide 321171-86-2P, N-Cyclopropylmethoxy-2-(4-iodo-2-  
 methylphenylamino)-4-phenylsulfamoylbenzamide 321171-89-5P,  
 N-Cyclopropylmethoxy-2-(4-iodo-2-methylphenylamino)-4-(pyridin-3-  
 ylsulfamoyl)benzamide 321171-92-0P, N-Cyclopropylmethoxy-2-(4-iodo-2-  
 methylphenylamino)-4-[(pyridin-3-ylmethyl)sulfamoyl]benzamide  
 321171-95-3P, 4-(Bispyridin-3-ylmethylsulfamoyl)-N-cyclopropylmethoxy-2-(4-  
 iodo-2-methylphenylamino)benzamide 321171-98-6P, N-Cyclopropylmethoxy-4-

[(2-hydroxyethyl)pyridin-4-ylmethylsulfamoyl]-2-(4-iodo-2-methylphenylamino)benzamide 321172-01-4P, N-Cyclopropylmethoxy-2-(4-iodo-2-methylphenylamino)-4-(methylpyridin-3-ylmethylsulfamoyl)benzamide 321172-04-7P, N-Cyclopropylmethoxy-4-[(3-diethylaminopropyl)pyridin-3-ylmethylsulfamoyl]-2-(4-iodo-2-methylphenylamino)benzamide 321172-07-0P, 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-4-phenylsulfamoylbenzamide 321172-10-5P, 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-4-(pyridin-3-ylsulfamoyl)benzamide 321172-14-9P, 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-4-[(pyridin-3-ylmethyl)sulfamoyl]benzamide 321172-18-3P, 4-(Bispyridin-3-ylmethylsulfamoyl)-2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxybenzamide 321172-21-8P, 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-4-[(2-hydroxyethyl)pyridin-4-ylmethylsulfamoyl]benzamide 321172-25-2P, 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-4-(methylpyridin-3-ylmethylsulfamoyl)benzamide 321172-29-6P, 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-4-[(3-diethylaminopropyl)pyridin-3-ylmethylsulfamoyl]benzamide 321172-45-6P 321858-06-4P, N-Allyloxy-2-(2-chloro-4-iodophenylamino)-3,4-difluoro-5-(methoxymethylsulfamoyl)benzamide

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of (phenylamino)benzenesulfonamides and (phenylamino)benzamides as MEK inhibitors for treatment of chronic pain)

IT 148553-50-8, Pregabalin 212631-61-3, PD 198306 212631-79-3, PD 184352 284030-47-3, PD 254552

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of (phenylamino)benzenesulfonamides and (phenylamino)benzamides as MEK inhibitors for treatment of chronic pain)

IT 142805-58-1, MEK kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(preparation of (phenylamino)benzenesulfonamides and (phenylamino)benzamides as MEK inhibitors for treatment of chronic pain)

IT 100-01-6, 4-Nitroaniline, reactions 100-16-3, 4-Nitrophenylhydrazine 104-96-1 123-54-6, 2,4-Pentanedione, reactions 288-13-1, Pyrazole 350-46-9, 1-Fluoro-4-nitrobenzene 696-59-3, 2,5-Dimethoxytetrahydrofuran 1583-58-0, 2,4-Difluorobenzoic acid 17061-62-0, Bis-4-methoxybenzylamine 42016-93-3, 2-Chloro-4-iodoaniline 61079-72-9, 2,3,4-Trifluorobenzoic acid 74124-04-2, O-Cyclopropylmethylhydroxylamine hydrochloride 175278-08-7, 2,3,4-Trifluorobenzenesulfonyl chloride 285127-06-2, 1-Dimethylsulfamoyl-2,3,4-trifluorobenzene 321166-92-1, Lithium 5-bis(4-methoxybenzyl)sulfamoyl-2,3,4-trifluorobenzoate 321166-98-7, Lithium 2-chloro-4-iodoanilide 321167-01-5, Lithium 5-dimethylsulfamoyl-2,3,4-trifluorobenzoate

RL: RCT (Reactant); RACT (Reactant or reagent)

(starting material; preparation of (phenylamino)benzenesulfonamides and (phenylamino)benzamides as MEK inhibitors for treatment of chronic pain)

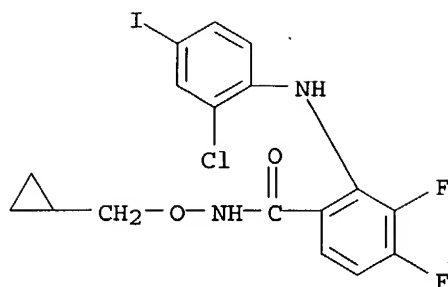
IT 212631-79-3, PD 184352

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of (phenylamino)benzenesulfonamides and (phenylamino)benzamides as MEK inhibitors for treatment of chronic pain)

RN 212631-79-3 HCAPLUS

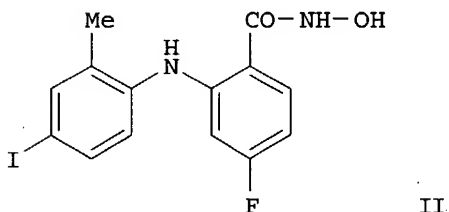
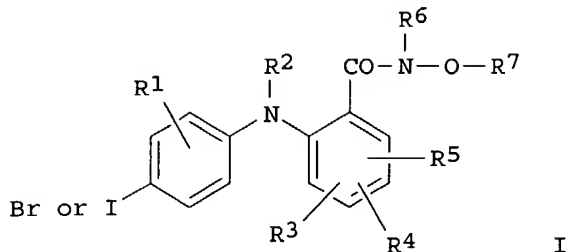
CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 10 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN  
 AN 2001:63819 HCAPLUS  
 DN 134:131317  
 ED Entered STN: 26 Jan 2001  
 TI Preparation of 2-phenylaminobenzamides and analogs as MEK inhibitors for  
 the treatment of chronic pain  
 IN Dixon, Alistair; Lee, Kevin; Pinnock, Robert Denham  
 PA Warner-Lambert Company, USA  
 SO PCT Int. Appl., 132 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 IC ICM A61K031-00  
 CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)  
 Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001005392	A2	20010125	WO 2000-US18347	20000705 <--
	WO 2001005392	A3	20010719		
	W:	AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	TR 200200082	T2	20020422	TR 2002-200200082	20000705 <--
	EP 1202726	A2	20020508	EP 2000-943383	20000705 <--
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL			
	NZ 515567	A	20040326	NZ 2000-515567	20000705 <--
	ZA 2001009907	A	20030228	ZA 2001-9907	20011130 <--
PRAI	US 1999-144292P	P	19990716 <--		
	WO 2000-US18347	W	20000705 <--		
OS	MARPAT 134:131317				
GI					



- AB The title compds. (I) [wherein R1 = H, OH, alkyl, alkoxy, halo, CF3, or CN; R2 = H; R3, R4, and R5 = independently H, OH, halo, CF3, alkyl, alkoxy, NO2, CN, or (O or NH)<sub>m</sub>(CH<sub>2</sub>)<sub>n</sub>R9; R9 = H, OH, CO<sub>2</sub>H, or NR<sub>10</sub>R<sub>11</sub>; m = 0 or 1; n = 0-4; R10 and R11 = independently H, alkyl, or taken together with the N to which they are attached form a heterocycle; R6 = H, (cyclo)alkyl, acyl, aryl, or aralkyl; R7 = H, (cyclo)alkyl, alkenyl, alkynyl, or heterocyclyl] were prepared using conventional and combinatorial synthetic methods for the treatment of chronic pain. For example, 2,4-difluorobenzoic acid in THF was added to a solution of 2-amino-5-iodotoluene and Li diisopropylamide in THF/heptane/EtPh to give 4-fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid (47%). Treatment of the acid with O-(tetrahydro-2H-pyran-2-yl)hydroxylamine and diisopropylethylamine in THF/CH<sub>2</sub>Cl<sub>2</sub> in the presence of PyBOP afforded the O-protected intermediate, which was dissolved in ethanolic HCl to give the title N-hydroxybenzamide (II) in 23% yield. Biol. assays indicated that MEK inhibitors exert an antiallodynic effect in CCI-induced neuropathic rats when administered intrathecally and that the antiallodynic effect correlates with the affinity of the compds.
- ST phenylamino benzamide conventional combinatorial prepn mek inhibitor;  
benzamide prepn analgesic chronic pain treatment
- IT Pain  
Skin, disease  
(allodynia, treatment; preparation of 2-phenylaminobenzamide and 2-phenylaminobenzoic acid MEK inhibitors by conventional and combinatorial synthetic methods for treatment of chronic pain)
- IT Vitamins  
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)  
(avitaminosis, treatment of pain associated with; preparation of 2-phenylaminobenzamide and 2-phenylaminobenzoic acid MEK inhibitors by conventional and combinatorial synthetic methods for treatment of chronic pain)
- IT Kidney, disease  
(failure, treatment of pain associated with; preparation of 2-phenylaminobenzamide and 2-phenylaminobenzoic acid MEK inhibitors by conventional and combinatorial synthetic methods for treatment of chronic pain)
- IT Analgesics  
Combinatorial library  
(preparation of 2-phenylaminobenzamide and 2-phenylaminobenzoic acid MEK

inhibitors by conventional and combinatorial synthetic methods for treatment of chronic pain)

IT Pain

(treatment of idiopathic and post-operative; preparation of 2-phenylaminobenzamide and 2-phenylaminobenzoic acid MEK inhibitors by conventional and combinatorial synthetic methods for treatment of chronic pain)

IT Alcoholism

Arthritis

Hypothyroidism

Inflammation

(treatment of pain associated with; preparation of 2-phenylaminobenzamide

and

2-phenylaminobenzoic acid MEK inhibitors by conventional and combinatorial synthetic methods for treatment of chronic pain)

IT 57381-34-7P, 5-Chloro-2-fluorobenzonitrile 96515-79-6P, 5-Chloro-2-fluorobenzaldehyde 212631-82-8P, 5-Chloro-2-fluorobenzaldehyde oxime 212631-83-9P, 5-(5-Chloro-2-fluorophenyl)-1H-tetrazole 212631-84-0P, 4-Fluoro-N-((tetrahydro-2H-pyran-2-yl)oxy)-2-(4-iodo-2-methylphenylamino)benzamide 212631-85-1P, 5-Bromo-2,3,4-trifluorobenzoic acid

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of 2-phenylaminobenzamide and 2-phenylaminobenzoic acid MEK inhibitors by conventional and combinatorial synthetic methods for treatment of chronic pain)

IT 212628-43-8P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-46-1P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-48-3P, 5-Chloro-2-(4-iodo-2-methylphenylamino)benzoic acid 212631-86-2P, 5-Bromo-3,4-difluoro-N-((tetrahydro-2H-pyran-2-yl)oxy)-2-(4-iodo-2-methylphenylamino)benzamide

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of 2-phenylaminobenzamide and 2-phenylaminobenzoic acid MEK inhibitors by conventional and combinatorial synthetic methods for treatment of chronic pain)

IT 212628-44-9P, 3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-45-0P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-47-2P, 5-Chloro-2-(2-chloro-4-iodophenylamino)benzoic acid 212628-49-4P, Sodium 5-Chloro-2-(4-iodo-2-methylphenylamino)benzoate 212628-50-7P, 5-Bromo-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-51-8P, 2-(2-Chloro-4-iodophenylamino)-5-nitrobenzoic acid 212628-52-9P, 4-Fluoro-2-(3-fluoro-4-iodo-2-methylphenylamino)benzoic acid 212628-53-0P, 2-(4-Iodo-2-methylphenylamino)-5-nitrobenzoic acid 212628-54-1P, 2-(2-Fluoro-4-iodophenylamino)-5-nitrobenzoic acid 212628-55-2P, 2-(4-Bromo-2-methylphenylamino)-4-fluorobenzoic acid 212628-56-3P, 2-(2-Bromo-4-iodophenylamino)-5-nitrobenzoic acid 212628-57-4P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluorobenzoic acid 212628-58-5P, 3-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-59-6P, 3,4-Difluoro-2-(4-iodo-2-methoxyphenylamino)benzoic acid 212628-60-9P, 4-Chloro-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-61-0P, 2-(4-Iodo-2-methylphenylamino)benzoic acid 212628-62-1P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-63-2P, 5-Iodo-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-69-8P, 2-(4-Iodophenylamino)-5-methoxybenzoic acid 212628-72-3P, 2-Fluoro-6-(4-iodo-2-methylphenylamino)benzoic acid 212628-73-4P, 4-Fluoro-2-(2,3-dimethyl-4-iodophenylamino)benzoic acid 212628-74-5P, 5-Methyl-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-75-6P, 2-Chloro-6-(4-iodo-2-methylphenylamino)benzoic acid 212628-76-7P, 2-(4-Iodo-2-methylphenylamino)-4-nitrobenzoic acid 212628-77-8P, 5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide

212628-78-9P, 4-Methoxy-N-(4-methoxyphenyl)-3-nitrobenzamide  
212628-79-0P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)benzamide  
212628-80-3P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-methylbenzamide  
212628-81-4P, N-Ethyl-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide  
212628-82-5P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N,N-dimethylbenzamide 212628-83-6P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(1H-tetrazol-5-yl)benzamide 212628-84-7P, 5-Bromo-2-(4-iodo-2-methylphenylamino)benzamide 212628-85-8P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N,N-dimethylbenzamide 212628-86-9P, [5-Chloro-2-(4-iodo-2-methylphenylamino)benzoylamino]acetic acid  
212628-87-0P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-propylbenzamide  
212628-88-1P, 5-Bromo-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212628-89-2P, N,N-Diethyl-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212628-90-5P, 4-Fluoro-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212628-91-6P, N,N-Diethyl-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212628-92-7P, N-Butyl-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212628-93-8P, 5-Chloro-N,N-diethyl-2-(4-iodo-2-methylphenylamino)benzamide 212628-94-9P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N,N-dimethylbenzamide 212628-95-0P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)benzyl alcohol 212628-96-1P, [5-Chloro-2-(4-iodo-2-methylphenylamino)phenyl]methanol 212628-97-2P, [2-(4-Iodo-2-methylphenylamino)-5-nitrophenyl]methanol 212628-98-3P, [5-Bromo-2-(4-iodo-2-methylphenylamino)phenyl]methanol 212628-99-4P, 5-Bromo-3,4-difluoro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-00-0P, N-(2,3-Dihydroxypropyl)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-01-1P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-02-2P, 3,4-Difluoro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-03-3P, N-(2,3-Dihydroxypropyl)-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-04-4P, 3,4-Difluoro-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-05-5P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-06-6P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyridin-4-ylethyl)benzamide 212629-07-7P, 4-Fluoro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-08-8P, 5-Bromo-N-(3-dimethylaminopropyl)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-09-9P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-10-2P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-11-3P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-12-4P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyridin-4-ylethyl)benzamide 212629-13-5P, N-(3-Dimethylaminopropyl)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-14-6P, N-Benzyl-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-15-7P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-hydroxyethyl)benzamide 212629-16-8P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-17-9P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-18-0P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-19-1P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-thiophen-2-ylethyl)benzamide 212629-20-4P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-21-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-morpholin-4-ylethyl)benzamide 212629-22-6P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-pyridin-4-ylmethylbenzamide 212629-23-7P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-pyridin-4-ylmethylbenzamide 212629-24-8P, 2-(4-Bromo-2-methylphenylamino)-N-(3-dimethylaminopropyl)-3,4-difluorobenzamide 212629-25-9P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-pyridin-4-ylmethylbenzamide 212629-26-0P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyridin-4-ylethyl)benzamide 212629-27-1P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-pyridin-4-

ylethyl)benzamide 212629-28-2P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(3-hydroxypropyl)benzamide 212629-29-3P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-30-6P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-phenethylbenzamide 212629-31-7P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-thiophen-2-ylethyl)benzamide 212629-32-8P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-pyridin-4-ylmethylbenzamide 212629-33-9P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-phenethylbenzamide 212629-34-0P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-piperidin-1-ylethyl)benzamide 212629-35-1P, 5-Chloro-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-36-2P, 5-Fluoro-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-37-3P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-pyridin-4-ylmethylbenzamide 212629-38-4P, 5-Bromo-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-39-5P, 5-Chloro-N-(2-diethylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-40-8P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-41-9P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-42-0P, 5-Bromo-N-(2-diethylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-43-1P, N-[2-[Bis(2-hydroxyethyl)amino]ethyl]-5-chloro-2-(4-iodo-2-methylphenylamino)benzamide 212629-44-2P, N-[2-[Bis(2-hydroxyethyl)amino]ethyl]-5-bromo-2-(4-iodo-2-methylphenylamino)benzamide 212629-45-3P, 2-(4-Iodo-2-methylphenylamino)-5-nitrobenzoic acid phenethyl ester 212629-46-4P, N-[3-[4-(2-Hydroxyethyl)piperazin-1-yl]propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-47-5P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-pyridin-4-ylmethylbenzamide 212629-48-6P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-50-0P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-52-2P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-54-4P, 5-Chloro-N-(3-dimethylaminopropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-56-6P, N-[2-[Bis(2-hydroxyethyl)amino]ethyl]-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-58-8P, 5-Chloro-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-60-2P, 5-Chloro-N-(3-diethylamino-2-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-62-4P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-64-6P, 5-Bromo-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-66-8P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-68-0P, N-[2-[Bis(2-hydroxyethyl)amino]ethyl]-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212629-69-1P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-71-5P, 5-Chloro-N-(3-diethylaminopropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-73-7P, 5-Chloro-N-(2-diisopropylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-75-9P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-77-1P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-(2-piperidin-1-yl-ethyl)benzamide 212629-78-2P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-piperazin-1-ylethyl)benzamide 212629-79-3P, N-(2-Diethylaminoethyl)-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-80-6P, 5-Bromo-N-(3-dimethylaminopropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-81-7P, N-(3-Hydroxypropyl)-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212629-82-8P, 5-Fluoro-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-83-9P, N-(3-Diethylaminopropyl)-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-84-0P, N-(3-Diethylaminopropyl)-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212629-85-1P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-86-2P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-(3-piperidin-1-yl-propyl)benzamide 212629-87-3P, 5-Bromo-N-(2-diisopropylaminoethyl)-2-(4-iodo-2-

methylphenylamino)benzamide 212629-88-4P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-89-5P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-90-8P, N-(3-Diethylamino-2-hydroxypropyl)-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-91-9P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-92-0P, N-(3-Dimethylaminopropyl)-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212629-93-1P, N-(2-Diisopropylaminoethyl)-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-94-2P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)thiobenzoic acid S-phenethyl ester 212629-95-3P, 5-Chloro-2-(4-iodo-2-methylphenylamino)thiobenzoic acid S-phenethyl ester 212629-98-6P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)thiobenzoic acid S-benzyl ester 212629-99-7P, 5-Chloro-2-(4-iodo-2-methylphenylamino)thiobenzoic acid S-benzyl ester 212630-00-7P, N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-03-0P, 5-Fluoro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212630-04-1P, N-Benzyloxy-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-05-2P, N-Benzyloxy-5-bromo-2-(4-iodo-2-methylphenylamino)benzamide 212630-06-3P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-(4-sulfamoylbenzyl)benzamide 212630-07-4P, N-(2-Hydroxyethyl)-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-08-5P, N-(2-Hydroxyethyl)-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-09-6P, 2-(4-Iodo-2-methylphenylamino)-N-methyl-5-nitro-N-phenylbenzamide 212630-10-9P, 5-Chloro-N-cyclopropyl-2-(4-iodo-2-methylphenylamino)benzamide 212630-11-0P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-methyl-N-phenylbenzamide 212630-12-1P, N-Allyl-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-13-2P, N-Benzyloxy-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-14-3P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(4-sulfamoylbenzyl)benzamide 212630-15-4P, N-Allyl-5-chloro-2-(4-iodo-2-methylphenylamino)benzamide 212630-16-5P, N-Cyclopropyl-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-17-6P, 5-Bromo-N-cyclopropyl-2-(4-iodo-2-methylphenylamino)benzamide 212630-18-7P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-methyl-N-phenylbenzamide 212630-19-8P, 5-Iodo-2-(4-iodo-2-methylphenylamino)-N-(4-sulfamoylbenzyl)benzamide 212630-20-1P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(4-sulfamoylbenzyl)benzamide 212630-21-2P, N-Allyl-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-22-3P, N-Allyl-5-bromo-2-(4-iodo-2-methylphenylamino)benzamide 212630-23-4P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-24-5P, N-Cyclopropyl-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-25-6P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-methyl-N-phenylbenzamide 212630-26-7P, N-Benzyloxy-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-27-8P, N-Cyclohexyl-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-28-9P, N-Allyl-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-29-0P, 5-Iodo-2-(4-iodo-2-methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-30-3P, 2-(4-Iodo-2-methylphenylamino)-N-(3-methylbenzyl)-5-nitrobenzamide 212630-31-4P, 5-Iodo-2-(4-iodo-2-methylphenylamino)-N-methyl-N-phenylbenzamide 212630-32-5P, N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-33-6P, 5-Chloro-N-cyclohexyl-2-(4-iodo-2-methylphenylamino)benzamide 212630-34-7P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-35-8P, 5-Bromo-N-cyclohexyl-2-(4-iodo-2-methylphenylamino)benzamide 212630-36-9P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-37-0P, N-Cyclohexyl-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-38-1P, [4-Chloro-2-(1H-tetrazol-5-yl)phenyl](4-iodo-2-methylphenyl)amine 212630-39-2P, [4-Iodo-2-methylphenyl]-[2-(1H-tetrazol-5-yl)phenyl]amine 212630-40-5P, [4-Nitro-2-(1H-tetrazol-5-yl)phenyl](4-iodo-2-methylphenyl)amine 212630-41-6P, 4-Fluoro-N-hydroxy-2-(4-iodo-2-methylphenylamino)benzamide 212630-42-7P, 5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methylphenylamino)benzamide 212630-43-8P, 2-(4-Bromo-2-

methylphenylamino)-4-fluoro-N-hydroxybenzamide 212630-44-9P,  
5-Chloro-N-hydroxy-2-(4-iodo-2-methylphenylamino)-N-methylbenzamide  
212630-45-0P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(terahydropyran-2-  
yloxy)benzamide 212630-46-1P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-  
methoxybenzamide 212630-47-2P, 4-Fluoro-N-hydroxy-2-(4-fluoro-2-  
methylphenylamino)benzamide 212630-48-3P, 4-Fluoro-N-hydroxy-2-(2-methyl  
phenylamino)benzamide 212630-49-4P, 4-Fluoro-2-(4-fluoro-2-  
methylphenylamino)-N-(terahydro-2H-pyran-2-yloxy)benzamide 212630-50-7P,  
4-Fluoro-N-hydroxy-2-(4-chloro-2-methylphenylamino)benzamide  
212630-51-8P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-  
phenylmethoxybenzamide 212630-52-9P, 4-Fluoro-2-(4-iodo-2-  
methylphenylamino)-N-methoxybenzamide 212630-53-0P, 3,4-Difluoro-2-(4-  
iodo-2-methylphenylamino)-N-methoxybenzamide 212630-54-1P,  
2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-methoxybenzamide  
212630-55-2P, 2-(4-Bromo-2-methylphenylamino)-N-ethoxy-3,4-  
difluorobenzamide 212630-56-3P, 5-Bromo-N-ethoxy-3,4-difluoro-2-(4-iodo-  
2-methylphenylamino)benzamide 212630-57-4P, 3,4-Difluoro-2-(4-iodo-2-  
methylphenylamino)-N-isopropoxybenzamide 212630-58-5P,  
2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-isopropoxybenzamide  
212630-59-6P, 4-Fluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-60-9P, 3,4-Difluoro-N-(furan-3-  
ylmethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 212630-61-0P,  
2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(furan-3-  
ylmethoxy)benzamide 212630-62-1P, 5-Bromo-3,4-difluoro-N-(furan-3-  
ylmethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 212630-63-2P,  
5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-64-3P, 4-Fluoro-2-(4-iodo-2-  
methylphenylamino)-N-(prop-2-ynyloxy)benzamide 212630-65-4P,  
3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(prop-2-ynyloxy)benzamide  
212630-66-5P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(1-methylprop-  
2-ynyloxy)benzamide 212630-67-6P, 2-(4-Bromo-2-methylphenylamino)-3,4-  
difluoro-N-(1-methylprop-2-ynyloxy)benzamide 212630-68-7P,  
N-(But-3-ynyloxy)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide  
212630-69-8P, 2-(4-Bromo-2-methylphenylamino)-N-(but-3-ynyloxy)-3,4-  
difluorobenzamide 212630-70-1P, 5-Bromo-N-(but-3-ynyloxy)-3,4-difluoro-2-  
(4-iodo-2-methylphenylamino)benzamide 212630-71-2P, 3,4-Difluoro-2-(4-  
iodo-2-methylphenylamino)-N-(3-phenylprop-2-ynyloxy)benzamide  
212630-72-3P, 3,4-Difluoro-2-(4-bromo-2-methylphenylamino)-N-(3-phenylprop-  
2-ynyloxy)benzamide 212630-73-4P, 3,4-Difluoro-N-[3-(3-fluorophenyl)prop-  
2-ynyloxy]-2-(4-iodo-2-methylphenylamino)benzamide 212630-74-5P,  
2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-[3-(3-fluorophenyl)prop-2-  
ynyloxy]benzamide 212630-75-6P, 3,4-Difluoro-N-[3-(2-fluorophenyl)prop-2-  
ynyloxy]-2-(4-iodo-2-methylphenylamino)benzamide 212630-76-7P,  
5-Bromo-3,4-difluoro-N-[3-(2-fluorophenyl)-prop-2-ynyloxy]-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-77-8P, 3,4-Difluoro-2-(4-iodo-2-  
methylphenylamino)-N-(3-methyl-5-phenylpent-2-en-4-ynyloxy)benzamide  
212630-78-9P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(3-methyl-5-  
phenylpent-2-en-4-ynyloxy)benzamide 212630-79-0P, N-Ethoxy-3,4-difluoro-  
2-(4-iodo-2-methylphenylamino)benzamide 212630-80-3P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-propoxybenzamide 212630-81-4P,  
3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-propoxybenzamide  
212630-82-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-  
propoxybenzamide 212630-83-6P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-  
methylphenylamino)-N-propoxybenzamide 212630-84-7P, 4-Fluoro-2-(4-iodo-2-  
methylphenylamino)-N-isopropoxybenzamide 212630-85-8P,  
5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-isopropoxybenzamide  
212630-86-9P, N-Cyclobutyloxy-3,4-difluoro-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-87-0P, 2-(4-Bromo-2-  
methylphenylamino)-N-cyclobutyloxy-3,4-difluorobenzamide 212630-88-1P,  
N-Cyclopentyloxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide  
212630-89-2P, 2-(4-Bromo-2-methylphenylamino)-N-cyclopentyloxy-3,4-  
difluorobenzamide 212630-90-5P, N-Cyclopropylmethoxy-4-fluoro-2-(4-iodo-  
2-methylphenylamino)benzamide 212630-91-6P, N-Cyclopropylmethoxy-3,4-

difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-92-7P,  
 2-(4-Bromo-2-methylphenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide  
 212630-94-9P, 5-Bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-  
 methylphenylamino)benzamide 212630-96-1P, 4-Fluoro-2-(4-iodo-2-  
 methylphenylamino)-N-(2-phenoxyethoxy)benzamide 212630-98-3P,  
 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-phenoxyethoxy)benzamide  
 212630-99-4P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-  
 phenoxyethoxy)benzamide 212631-00-0P, 4-Fluoro-2-(4-iodo-2-  
 methylphenylamino)-N-(thiophen-2-ylmethoxy)benzamide 212631-01-1P,  
 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(thiophen-2-  
 ylmethoxy)benzamide 212631-02-2P, 2-(4-Bromo-2-methylphenylamino)-3,4-  
 difluoro-N-(thiophen-2-ylmethoxy)benzamide 212631-03-3P,  
 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-methylallyloxy)benzamide  
 212631-04-4P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-  
 methylallyloxy)benzamide 212631-05-5P, 2-(4-Bromo-2-methylphenylamino)-  
 3,4-difluoro-N-(2-methylallyloxy)benzamide 212631-06-6P,  
 N-(But-2-enyloxy)-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide  
 212631-07-7P, N-(But-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-  
 methylphenylamino)benzamide

RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);  
 BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-phenylaminobenzamide and 2-phenylaminobenzoic acid MEK  
 inhibitors by conventional and combinatorial synthetic methods for  
 treatment of chronic pain)

IT 212631-08-8P, 2-(4-Bromo-2-methylphenylamino)-N-(but-2-enyloxy)-3,4-  
 difluorobenzamide 212631-09-9P, 2-(4-Bromo-2-methylphenylamino)-N-(4,4-  
 dimethyl-2-pentynyloxy)-3,4-difluorobenzamide 212631-13-5P,  
 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(prop-2-enyloxy)benzamide  
 212631-15-7P, N-Cyclopentynyloxy-4-fluoro-2-(4-iodo-2-  
 methylphenylamino)benzamide 212631-28-2P, 5-Bromo-N-butoxy-3,4-difluoro-  
 2-(4-iodo-2-methylphenylamino)benzamide 212631-29-3P,  
 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(3-methylbut-2-  
 enyloxy)benzamide 212631-30-6P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-  
 methylphenylamino)-N-(3-methylpent-2-en-4-ynyloxy)benzamide  
 212631-32-8P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(prop-  
 2-ynyloxy)benzamide 212631-33-9P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-  
 methylphenylamino)-N-[3-(3-methoxyphenyl)prop-2-ynyloxy]benzamide  
 212631-34-0P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-  
 (thiophen-2-ylmethoxy)benzamide 212631-35-1P, 5-Bromo-3,4-difluoro-2-(4-  
 iodo-2-methylphenylamino)-N-(pyridin-3-ylmethoxy)benzamide 212631-36-2P,  
 5-Chloro-N-hydroxy-2-(4-iodo-2-methylphenylamino)benzamide 212631-37-3P,  
 4-Bromo-2-(4-iodo-2-methylphenylamino)-N-phenylmethoxybenzamide  
 212631-38-4P, 5-Fluoro-N-hydroxy-2-(4-iodo-2-methylphenylamino)benzamide  
 212631-39-5P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(tetrahydropyran-2-  
 yloxy)benzamide 212631-40-8P, 3,4,5-Trifluoro-N-hydroxy-2-(4-iodo-2-  
 methylphenylamino)benzamide 212631-41-9P, 5-Chloro-3,4-difluoro-N-  
 hydroxy-2-(4-iodo-2-methylphenylamino)benzamide 212631-42-0P,  
 5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-N-hydroxybenzamide  
 212631-43-1P, N-Hydroxy-2-(4-iodo-2-methylphenylamino)-4-nitrobenzamide  
 212631-44-2P, 3,4,5-Trifluoro-2-(2-fluoro-4-iodophenylamino)-N-  
 hydroxybenzamide 212631-45-3P, 5-Chloro-3,4-difluoro-2-(2-fluoro-4-  
 iodophenylamino)-N-hydroxybenzamide 212631-46-4P, 5-Bromo-2-(2-chloro-4-  
 iodophenylamino)-3,4-difluoro-N-hydroxybenzamide 212631-47-5P,  
 2-(2-Fluoro-4-iodophenylamino)-N-hydroxy-4-nitrobenzamide 212631-48-6P,  
 2-(2-Chloro-4-iodophenylamino)-3,4,5-trifluoro-N-hydroxybenzamide  
 212631-49-7P, 5-Chloro-2-(2-chloro-4-iodophenylamino)-3,4-difluoro-N-  
 hydroxybenzamide 212631-50-0P, 5-Bromo-2-(2-bromo-4-iodophenylamino)-3,4-  
 difluoro-N-hydroxybenzamide 212631-51-1P, 2-(2-Chloro-4-iodophenylamino)-  
 N-hydroxy-4-methylbenzamide 212631-52-2P, 2-(2-Bromo-4-iodophenylamino)-  
 3,4,5-trifluoro-N-hydroxybenzamide 212631-54-4P, 2-(2-Bromo-4-  
 iodophenylamino)-N-hydroxy-4-nitrobenzamide 212631-55-5P,  
 4-Fluoro-2-(2-fluoro-4-iodophenylamino)-N-hydroxybenzamide 212631-56-6P,

3,4-Difluoro-2-(2-fluoro-4-iodophenylamino)-N-hydroxybenzamide  
212631-57-7P, 2-(2-Chloro-4-iodophenylamino)-4-fluoro-N-hydroxybenzamide  
212631-58-8P, 2-(2-Chloro-4-iodophenylamino)-3,4-difluoro-N-  
hydroxybenzamide 212631-59-9P, 2-(2-Bromo-4-iodophenylamino)-4-fluoro-N-  
hydroxybenzamide 212631-60-2P, 2-(2-Bromo-4-iodophenylamino)-3,4-  
difluoro-N-hydroxybenzamide 212631-61-3P, N-Cyclopropylmethoxy-3,4,5-  
trifluoro-2-(4-iodo-2-methylphenylamino)benzamide 212631-62-4P,  
5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-  
methylphenylamino)benzamide 212631-63-5P, 5-Bromo-N-cyclopropylmethoxy-  
3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzamide 212631-64-6P,  
N-Cyclopropylmethoxy-2-(4-iodo-2-methylphenylamino)-4-nitrobenzamide  
212631-65-7P, N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(2-fluoro-4-  
iodophenylamino)benzamide 212631-66-8P, 5-Chloro-N-cyclopropylmethoxy-  
3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzamide 212631-67-9P,  
5-Bromo-2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-  
difluorobenzamide 212631-68-0P, N-Cyclopropylmethoxy-2-(2-fluoro-4-  
iodophenylamino)-4-nitrobenzamide 212631-69-1P, 2-(2-Chloro-4-  
iodophenylamino)-N-cyclopropylmethoxy-3,4,5-trifluorobenzamide  
212631-70-4P, 5-Chloro-2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-  
3,4-difluorobenzamide 212631-71-5P, 5-Bromo-2-(2-bromo-4-  
iodophenylamino)-N-ethoxy-3,4-difluorobenzamide 212631-72-6P,  
2-(2-Chloro-4-iodophenylamino)-N-ethoxy-4-nitrobenzamide 212631-73-7P,  
2-(2-Bromo-4-iodophenylamino)-N-cyclopropylmethoxy-3,4,5-  
trifluorobenzamide 212631-75-9P, 2-(2-Bromo-4-iodophenylamino)-N-  
cyclopropylmethoxy-4-nitrobenzamide 212631-76-0P, N-Cyclopropylmethoxy-4-  
fluoro-2-(2-fluoro-4-iodophenylamino)benzamide 212631-77-1P,  
N-Cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzamide  
212631-78-2P, 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-4-  
fluorobenzamide 212631-79-3P, 3,4-Difluoro-2-(2-chloro-4-  
iodophenylamino)-N-cyclopropylmethoxybenzamide 212631-80-6P,  
2-(2-Bromo-4-iodophenylamino)-N-cyclopropylmethoxy-4-fluorobenzamide  
212631-81-7P, 2-(2-Bromo-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-  
difluorobenzamide 219777-46-5P, N-(3-tert-Butylpropyn-2-yl)oxy-4-fluoro-  
2-(4-iodo-2-methylphenylamino)benzamide 219777-48-7P,  
4-Fluoro-N-hydroxy-2-(4-iodo-2-methylphenylamino)-N-isopropylbenzamide  
219777-50-1P, 4-Fluoro-N-hydroxy-2-(4-iodo-2-methylphenylamino)-N-  
methylbenzamide 219777-52-3P, 4-Fluoro-N-hydroxy-2-(4-iodo-2-  
methylphenylamino)-5-nitrobenzamide 219777-54-5P, 2-(2-Chloro-4-  
iodophenylamino)-N-hydroxy-4-nitrobenzamide 219777-58-9P,  
3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(tetrahydropyran-2-  
yloxy)benzamide 219777-60-3P, 3,4-Difluoro-N-hydroxy-2-(4-iodo-2-  
methylphenylamino)benzamide 219777-61-4P, 3,4-Difluoro-5-bromo-2-(4-iodo-  
2-methylphenylamino)-N-(2-piperidin-1-ylethoxy)benzamide 219777-92-1P,  
2-(2-Chloro-4-iodophenylamino)-4-fluoro-N-hydroxybenzamide hydrochloride  
salt 219777-97-6P, 2-(2-Chloro-4-iodophenylamino)-4-fluoro-N-  
(tetrahydropyran-2-yloxy)benzamide 219778-04-8P, 3,4-Difluoro-2-(2-  
chloro-4-iodophenylamino)-N-cyclobutylmethoxybenzamide 219778-06-0P,  
3,4-Difluoro-2-(2-chloro-4-iodophenylamino)-N-(tetrahydropyran-2-  
yloxy)benzamide 219778-09-3P, 5-Bromo-2-(2-chloro-4-iodophenylamino)-N-  
(2-dimethylaminoethoxy)-3,4-difluorobenzamide monohydrochloride salt  
219778-12-8P, 5-Bromo-N-(2-dimethylaminopropoxy)-3,4-difluoro-2-(4-iodo-2-  
methylphenylamino)benzamide 219778-19-5P, 5-Bromo-2-(2-chloro-4-  
iodophenylamino)-3,4-difluoro-N-(tetrahydropyran-2-yloxy)benzamide  
219778-24-2P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-  
morpholin-4-ylethoxy)benzamide 219778-35-5P, 5-Bromo-N-(2-  
diethylaminoethoxy)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide  
219778-40-2P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-  
isobutoxybenzamide 219778-43-5P, 5-Bromo-N-cyclohexylmethoxy-3,4-  
difluoro-2-(4-iodo-2-methylphenylamino)benzamide 219778-48-0P,  
5-Bromo-N-cyclopentylmethoxy-3,4-difluoro-2-(4-iodo-2-  
methylphenylamino)benzamide 219778-52-6P, 5-Bromo-N-cyclobutylmethoxy-  
3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 219794-13-5P,  
5-Bromo-2-(4-iodo-2-methylphenylamino)thiobenzoic acid S-benzyl ester

219794-21-5P, 2-(4-Iodo-2-methylphenylamino)-5-nitrothiobenzoic acid  
 S-benzyl ester 219796-61-9P, 2-(2-Chloro-4-iodophenylamino)-3-fluoro-4-(2-morpholin-4-ylethylamino)-5-nitrobenzoic acid 219796-66-4P,  
 4-Amino-2-(2-chloro-4-iodophenylamino)-3-fluoro-5-nitrobenzoic acid  
 219796-67-5P, 2,4-Bis(2-chloro-4-iodophenylamino)-3-fluoro-5-nitrobenzoic acid 219796-68-6P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrobenzoic acid 219796-71-1P, 2-(2,6-Difluoro-4-iodophenylamino)-3,4-difluorobenzoic acid 219796-73-3P, 2-(2-Chloro-4-iodophenylamino)-4-nitrobenzoic acid 219796-74-4P, 2-(2,4-Diiodophenylamino)-4-fluorobenzoic acid 219796-75-5P, 2-(2-Bromo-4-iodophenylamino)-4-fluorobenzoic acid 219796-76-6P, 4-Fluoro-2-(2-fluoro-4-iodophenylamino)benzoic acid 219796-77-7P, 2-(2-Chloro-4-iodophenylamino)-4-fluorobenzoic acid 219796-79-9P, 5-Bromo-2-(2-chloro-4-iodophenylamino)-3,4-difluorobenzoic acid 219800-81-4P,  
 2,3,5-Trifluoro-6-(4-iodo-2-methylphenylamino)-4-(4-methylpiperazin-1-yl)benzoic acid methyl ester dihydrofluoride salt 219800-86-9P,  
 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
 N',N'-dimethylhydrazide 219800-90-5P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid hydrazide 219802-06-9P,  
 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(4-methylpiperazin-1-yl)benzamide 277335-40-7P, 5-Bromo-2-(4-iodo-2-ethylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 277335-43-0P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylbenzyl)-N-[5-(3-methoxyphenyl)-3-methylpent-2-en-4-ynyloxy]benzamide 278610-42-7P, 5-Chloro-2-(2-chloro-4-iodophenylamino)-3,4-difluorobenzoic acid 278610-51-8P, 5-Chloro-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 284030-47-3P, 7-Fluoro-6-(4-iodo-2-methylphenylamino)1H-benzimidazole-5-carboxylic acid  
 cyclopropylmethoxyamide 303175-44-2P, 2-(2-Chloro-4-iodophenylamino)-3,4-difluorobenzoic acid 321438-66-8P, N-(2-Hydroxyethyl)-2-(4-iodo-2-ethylphenylamino)-5-nitrobenzamide 321438-67-9P, N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-methylphenylamino)benzamide potassium salt 321438-68-0P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-methoxybenzamide 321438-69-1P, 4-Fluoro-N-hydroxy-2-(4-iodo-2-methylphenylamino)benzamide hydrochloride salt 321438-70-4P,  
 2-(2-Chloro-4-iodophenylamino)-3,4-difluoro-N-(2-hydroxyethoxy)benzamide 321438-71-5P, 3,4-Difluoro-N-(2-hydroxyethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 321438-72-6P, 5-Bromo-2-(2-chloro-4-iodophenylamino)-3,4-difluoro-N-(3-hydroxypropoxy)benzamide 321438-73-7P, 2-(2-Chloro-4-iodophenylamino)-3,4,5-trifluoro-N-(3-hydroxypropoxy)benzamide 321438-74-8P, 2-(2-Chloro-4-iodophenylamino)-3,4,5-trifluoro-N-[2-(2-methoxyethoxy)ethoxy]benzamide 321438-75-9P,  
 2-(2-Chloro-4-iodophenylamino)-3,4-difluoro-N-(3-hydroxypropoxy)benzamide 321438-76-0P, 5-Bromo-3,4-difluoro-N-(3-hydroxypropoxy)-2-(4-iodo-2-methylphenylamino)benzamide 321438-77-1P, 3,4,5-Trifluoro-N-(3-hydroxypropoxy)-2-(4-iodo-2-methylphenylamino)benzamide 321438-78-2P,  
 3,4,5-Trifluoro-N-(2-hydroxyethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 321438-79-3P, 2-(2-Chloro-4-iodophenylamino)-3,4-difluoro-5-nitrobenzoic acid 321438-80-6P, 2-(2-Chloro-4-iodophenylamino)-3,4,5-trifluorobenzoic acid

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-phenylaminobenzamide and 2-phenylaminobenzoic acid MEK inhibitors by conventional and combinatorial synthetic methods for treatment of chronic pain)

IT 148553-50-8, Pregabalin 283602-39-1 285125-85-1

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of 2-phenylaminobenzamide and 2-phenylaminobenzoic acid MEK inhibitors by conventional and combinatorial synthetic methods for treatment of chronic pain)

IT 142805-58-1, MEK kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(preparation of 2-phenylaminobenzamide and 2-phenylaminobenzoic acid MEK inhibitors by conventional and combinatorial synthetic methods for treatment of chronic pain)

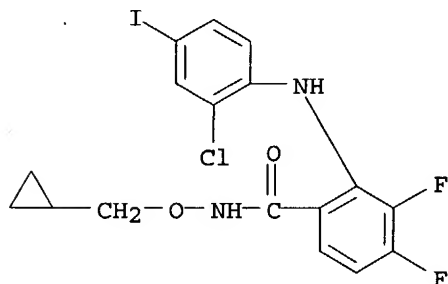
IT 352-33-0, 1-Chloro-4-fluorobenzene 1583-58-0, 2,4-Difluorobenzoic acid 6723-30-4, O-(Tetrahydro-2H-pyran-2-yl)hydroxylamine 13194-68-8, 2-Amino-5-iodotoluene 176317-02-5, 1-Bromo-2,3,4-trifluorobenzene

RL: RCT (Reactant); RACT (Reactant or reagent)  
(starting material; preparation of 2-phenylaminobenzamide and 2-phenylaminobenzoic acid MEK inhibitors by conventional and combinatorial synthetic methods for treatment of chronic pain)

IT 212631-79-3P, 3,4-Difluoro-2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxybenzamide  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of 2-phenylaminobenzamide and 2-phenylaminobenzoic acid MEK inhibitors by conventional and combinatorial synthetic methods for treatment of chronic pain)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 11 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:63818 HCAPLUS

DN 134:131540

ED Entered STN: 26 Jan 2001

TI Preparation of (2-heterocyclylphenyl)(4-iodophenyl)amines as MEK inhibitors for the treatment of chronic pain

IN Barrett, Stephen Douglas; Bridges, Alexander James; Tecle, Haile; Dixon, Alistair; Lee, Kevin; Pinnock, Robert Denham; Zhang, Lu-Yan

PA Warner-Lambert Company, USA

SO PCT Int. Appl., 104 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-00

CC 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001005391	A2	20010125	WO 2000-US18346	20000705 <--
	WO 2001005391	A3	20010719		

W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1202732 A2 20020508 EP 2000-943382 20000705 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL

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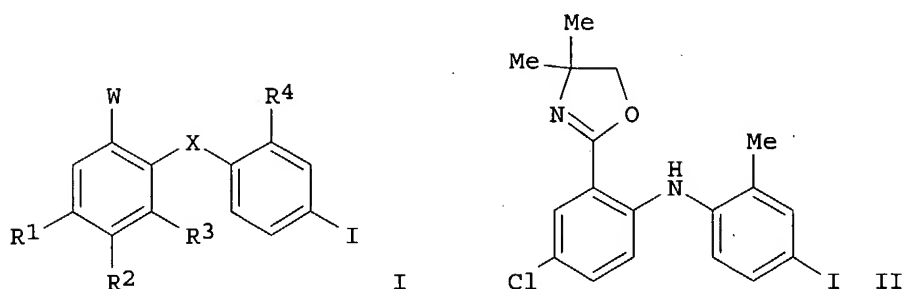
ZA 2001009903 A 20030228 ZA 2001-9903 20011130 <--

PRAI US 1999-144403P P 19990716 <--

WO 2000-US18346 W 20000705 <--

OS MARPAT 134:131540

GI



AB The title compds. (I) [wherein W = a variety of (un)substituted heterocycles; X = NRF; RF = H or (un)substituted alkyl; R1 and R2 = independently H, F, NO<sub>2</sub>, Br, Cl, or taken together with the benzene ring to which they are attached form an (un)substituted (iso)indole, benzofuran, benzothiophene, indazole, benzimidazole, or benzthiazole ring; or R1 = SO<sub>2</sub>NRGRH; R3 H or F; RG, RH, and R4 = independently H, Cl, or Me; R5 = H or (un)substituted alkyl] were prepared for the treatment of chronic pain. For example, cycloaddn. of 2-amino-2-methyl-1-propanol with 5-chloro-2-methoxybenzoic acid using SOCl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> gave 2-(5-chloro-2-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole (77%). Treatment with 4-iodo-2-methylaniline in THF in the presence of LDA afforded the diphenylamine (II) in 77% yield. Biol. assays indicated that MEK inhibitors exert an antiallodynic effect in CCI-induced neuropathic rats when administered intrathecally, and that the antiallodynic effect correlates with the affinity of the compds.

ST heterocyclylphenyl iodophenyl amine prepn mek inhibitor; phenylamine prepn analgesic; iodophenyl heterocyclylphenyl amine prepn chronic pain treatment

IT Pain

Skin, disease  
(allodynia, treatment; preparation of (2-heterocyclylphenyl)(4-iodophenyl)amines as MEK inhibitors for treatment of chronic pain)

IT Vitamins

RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)  
(avitaminosis, treatment of pain associated with; preparation of (2-heterocyclylphenyl)(4-iodophenyl)amines as MEK inhibitors for treatment of chronic pain)

IT Kidney, disease  
(failure, treatment of pain associated with; preparation of (2-heterocyclylphenyl)(4-iodophenyl)amines as MEK inhibitors for treatment of chronic pain)

IT Analgesics  
(preparation of (2-heterocyclylphenyl)(4-iodophenyl)amines as MEK inhibitors

- for treatment of chronic pain)
- IT Pain  
(treatment of idiopathic and post-operative; preparation of  
(2-heterocyclylphenyl) (4-iodophenyl) amines as MEK inhibitors for  
treatment of chronic pain)
- IT Alcoholism  
Arthritis  
Hypothyroidism  
Inflammation  
(treatment of pain associated with; preparation of (2-heterocyclylphenyl) (4-  
iodophenyl) amines as MEK inhibitors for treatment of chronic pain)
- IT 82400-14-4P, 2-(5-Chloro-2-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(intermediate; preparation of (2-heterocyclylphenyl) (4-iodophenyl) amines as  
MEK inhibitors for treatment of chronic pain)
- IT 284032-14-0P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
methyl ester 284032-17-3P, 2-[3,4-Difluoro-2-(4-iodo-2-  
methylphenylamino)benzoyl]hydrazinecarbothioamide 284033-41-6P,  
3,4-Difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid hydrazide  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU  
(Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT  
(Reactant or reagent); USES (Uses)  
(preparation of (2-heterocyclylphenyl) (4-iodophenyl) amines as MEK inhibitors  
for treatment of chronic pain)
- IT 219796-67-5P, 2,4-Bis(2-chloro-4-iodophenylamino)-3-fluoro-5-nitrobenzoic  
acid 284032-11-7P, [4-Chloro-2-(4,4-Dimethyl-4,5-dihydrooxazol-2-  
yl)phenyl]-(4-iodo-2-methylphenyl)amine hydrochloride salt 284032-12-8P,  
[2,3-Difluoro-6-(1H-tetrazol-5-yl)phenyl]-(4-iodo-2-methylphenyl)amine  
284032-13-9P, [6-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-2,3-difluorophenyl]-  
(4-iodo-2-methylphenyl)amine 284032-15-1P, 5-[3,4-Difluoro-2-(4-iodo-2-  
methylphenylamino)phenyl]-4H-[1,2,4]triazol-3-ylamine 284032-16-2P,  
5-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl][1,3,4]oxadiazol-2-  
ylamine 284032-18-4P, 5-[3,4-Difluoro-2-(4-iodo-2-  
methylphenylamino)phenyl]-4H-[1,2,4]triazole-3-thiol 284032-19-5P,  
(2,3-Difluoro-6-[1,3,4]oxadiazol-2-ylphenyl)-(4-iodo-2-methylphenyl)amine  
284032-20-8P, 5-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-  
[1,3,4]oxadiazole-2-thiol 284032-21-9P, [5-Fluoro-2-(1H-tetrazol-5-  
yl)phenyl]-(4-iodo-2-methylphenyl)amine 284032-22-0P,  
(4-Iodo-2-methylphenyl)-[2,3,4-trifluoro-6-(1H-tetrazol-5-yl)phenyl]amine  
284032-23-1P, [4-Bromo-2,3-difluoro-6-(1H-tetrazol-5-yl)phenyl]-(4-iodo-2-  
methylphenyl)amine 284032-24-2P, [5-Fluoro-4-nitro-2-(1H-tetrazol-5-  
yl)phenyl]-(4-iodo-2-methylphenyl)amine 284032-25-3P,  
[2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-5-fluorophenyl]-(4-iodo-2-  
methylphenyl)amine 284032-26-4P, [6-(4,4-Dimethyl-4,5-dihydrooxazol-2-  
yl)-2,3,4-trifluorophenyl]-(4-iodo-2-methylphenyl)amine 284032-27-5P,  
[4-Bromo-6-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-2,3-difluorophenyl]-(4-  
iodo-2-methylphenyl)amine 284032-28-6P, [2-(4,4-Dimethyl-4,5-  
dihydrooxazol-2-yl)-5-fluoro-4-nitrophenyl]-(4-iodo-2-methylphenyl)amine  
284032-29-7P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-  
[1,3,4]thiadiazol-2-ol 284032-30-0P, 5-[3,4-Difluoro-2-(4-iodo-2-  
methylphenylamino)phenyl]-[1,3,4]thiadiazol-2-ol 284032-31-1P,  
5-[3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]-[1,3,4]thiadiazol-  
2-ol 284032-32-2P, 5-[5-Bromo-3,4-difluoro-2-(4-iodo-2-  
methylphenylamino)phenyl]-[1,3,4]thiadiazol-2-ol 284032-33-3P,  
5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]-  
[1,3,4]thiadiazol-2-ol 284032-34-4P, 5-[4-Fluoro-2-(4-iodo-2-  
methylphenylamino)phenyl]-[1,3,4]oxadiazol-2-ol 284032-35-5P,  
5-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-[1,3,4]oxadiazol-2-  
ol 284032-36-6P, 5-[3,4,5-Trifluoro-2-(4-iodo-2-  
methylphenylamino)phenyl]-[1,3,4]oxadiazol-2-ol 284032-37-7P,  
5-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-

[1,3,4]oxadiazol-2-ol 284032-38-8P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]-[1,3,4]oxadiazol-2-ol 284032-39-9P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-4H-[1,2,4]triazol-3-ol 284032-40-2P, 5-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-4H-[1,2,4]triazol-3-ol 284032-41-3P, 5-[3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]-4H-[1,2,4]triazol-3-ol 284032-42-4P, 5-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-4H-[1,2,4]triazol-3-ol 284032-43-5P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]-4H-[1,2,4]triazol-3-ol 284032-44-6P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-[1,3,4]thiadiazol-2-ylamine 284032-45-7P, 5-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-[1,3,4]thiadiazol-2-ylamine 284032-46-8P, 5-[3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]-[1,3,4]thiadiazol-2-ylamine 284032-47-9P, 5-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-[1,3,4]thiadiazol-2-ylamine 284032-48-0P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]-[1,3,4]thiadiazol-2-ylamine 284032-49-1P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-[1,3,4]oxadiazol-2-ylamine 284032-50-4P, 5-[3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]-[1,3,4]oxadiazol-2-ylamine 284032-51-5P, 5-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-[1,3,4]oxadiazol-2-ylamine 284032-52-6P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]-[1,3,4]oxadiazol-2-ylamine 284032-53-7P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-4H-[1,2,4]triazol-3-ylamine 284032-54-8P, 5-[3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]-4H-[1,2,4]triazol-3-ylamine 284032-55-9P, 5-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-4H-[1,2,4]triazol-3-ylamine 284032-56-0P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]-4H-[1,2,4]triazol-3-ylamine 284032-57-1P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-[1,3,4]thiadiazole-2-thiol 284032-58-2P, 5-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-[1,3,4]thiadiazole-2-thiol 284032-59-3P, 5-[3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]-[1,3,4]thiadiazole-2-thiol 284032-60-6P, 5-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-[1,3,4]thiadiazole-2-thiol 284032-61-7P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]-[1,3,4]thiadiazole-2-thiol 284032-62-8P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-[1,3,4]oxadiazole-2-thiol 284032-63-9P, 5-[3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]-[1,3,4]oxadiazole-2-thiol 284032-64-0P, 5-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-[1,3,4]oxadiazole-2-thiol 284032-65-1P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]-[1,3,4]oxadiazole-2-thiol 284032-66-2P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-4H-[1,2,4]triazole-3-thiol 284032-67-3P, 5-[3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]-4H-[1,2,4]triazole-3-thiol 284032-68-4P, 5-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-4H-[1,2,4]triazole-3-thiol 284032-69-5P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]-4H-[1,2,4]triazole-3-thiol 284032-70-8P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]isothiazol-3-ol 284032-71-9P, 5-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl]isothiazol-3-ol 284032-72-0P, 5-[3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]isothiazol-3-ol 284032-73-1P, 5-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]isothiazol-3-ol 284032-74-2P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]isothiazol-3-ol 284032-75-3P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]isoxazol-3-ol 284032-76-4P, 5-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl]isoxazol-3-ol 284032-77-5P, 5-[3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]isoxazol-3-ol 284032-78-6P, 5-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]isoxazol-3-ol 284032-79-7P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]isoxazol-3-ol 284032-80-0P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-1H-pyrazol-

3-ol 284032-81-1P, 5-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-1H-pyrazol-3-ol 284032-82-2P, 5-[3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]-1H-pyrazol-3-ol 284032-83-3P, 5-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-1H-pyrazol-3-ol 284032-84-4P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]-1H-pyrazol-3-ol 284032-85-5P, 4-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]isothiazol-3-ol 284032-86-6P, 4-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl]isothiazol-3-ol 284032-87-7P, 4-[3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]isothiazol-3-ol 284032-88-8P, 4-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]isothiazol-3-ol 284032-89-9P, 4-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]isothiazol-3-ol 284032-90-2P, 4-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]isoxazol-3-ol 284032-91-3P, 4-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl]isoxazol-3-ol 284032-92-4P, 4-[3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]isoxazol-3-ol 284032-93-5P, 4-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]isoxazol-3-ol 284032-94-6P, 4-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]isoxazol-3-ol 284032-95-7P, 4-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-1-methyl-1H-pyrazol-3-ol 284032-96-8P, 4-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-1-methyl-1H-pyrazol-3-ol 284032-97-9P, 1-Methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]-1H-pyrazol-3-ol 284032-98-0P, 4-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-1-methyl-1H-pyrazol-3-ol 284032-99-1P, 4-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]-1-methyl-1H-pyrazol-3-ol 284033-00-7P, 5-[2-(2-Amino-4-iodophenylamino)-4-fluorophenyl]-1-methyl-1H-[1,2,3]triazol-4-ol 284033-01-8P, 5-[2-(2-Amino-4-iodophenylamino)-3,4-difluorophenyl]-1-methyl-1H-[1,2,3]triazol-4-ol 284033-02-9P, 5-[2-(2-Amino-4-iodophenylamino)-3,4,5-trifluorophenyl]-1-methyl-1H-[1,2,3]triazol-4-ol 284033-03-0P, 5-[2-(2-Amino-4-iodophenylamino)-5-bromo-3,4-difluorophenyl]-1-methyl-1H-[1,2,3]triazol-4-ol 284033-04-1P, 5-[2-(2-Amino-4-iodophenylamino)-4-fluoro-5-nitrophenyl]-1-methyl-1H-[1,2,3]triazol-4-ol 284033-05-2P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol 284033-06-3P, 5-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol 284033-07-4P, 3-Methyl-5-[3,4,5-trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]-3H-[1,2,3]triazol-4-ol 284033-08-5P, 5-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-3-methyl-3H-[1,2,3]triazol-4-ol 284033-09-6P, 5-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]-3-methyl-3H-[1,2,3]triazol-4-ol 284033-10-9P, 4-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-2-methyl-2H-pyrazol-3-ol 284033-11-0P, 4-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-2-methyl-2H-pyrazol-3-ol 284033-12-1P, 2-Methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]-2H-pyrazol-3-ol 284033-13-2P, 4-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-2-methyl-2H-pyrazol-3-ol 284033-14-3P, 4-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]-2-methyl-2H-pyrazol-3-ol 284033-15-4P, 1-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-4-methyl-1,4-dihydrotetrazol-5-one 284033-16-5P, 1-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-4-methyl-1,4-dihydrotetrazol-5-one 284033-17-6P, 1-Methyl-4-[3,4,5-trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]-1,4-dihydrotetrazol-5-one 284033-18-7P, 1-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-4-methyl-1,4-dihydrotetrazol-5-one 284033-20-1P, 1-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-1H-[1,2,3]triazol-4-ol 284033-21-2P, 1-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-1H-[1,2,3]triazol-4-ol 284033-22-3P, 1-[3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]-1H-[1,2,3]triazol-4-ol 284033-23-4P, 1-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-1H-[1,2,3]triazol-4-ol 284033-25-6P, 3-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-2H-isoxazol-5-one 284033-26-7P, 3-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-2H-

isoxazol-5-one 284033-27-8P, 3-[3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]-2H-isoxazol-5-one 284033-28-9P, 3-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-2H-isoxazol-5-one 284033-29-0P, 3-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]-2H-isoxazol-5-one 284033-30-3P, [5-Fluoro-2-(2-oxo-2,3-dihydro-[1,2,3,5]oxathiadiazol-4-yl)phenyl]-(4-iodo-2-methylphenyl)amine 284033-31-4P, [2,3-Difluoro-6-(2-oxo-2,3-dihydro-[1,2,3,5]oxathiadiazol-4-yl)phenyl]-(4-iodo-2-methylphenyl)amine 284033-32-5P, (4-Iodo-2-methylphenyl)-(2,3,4-trifluoro-6-(2-oxo-2,3-dihydro-[1,2,3,5]oxathiadiazol-4-yl)phenyl)amine 284033-33-6P, [4-Bromo-2,3-difluoro-6-(2-oxo-2,3-dihydro-[1,2,3,5]oxathiadiazol-4-yl)phenyl]-(4-iodo-2-methylphenyl)amine 284033-34-7P, [5-Fluoro-4-nitro-2-(2-oxo-2,3-dihydro-[1,2,3,5]oxathiadiazol-4-yl)phenyl]-(4-iodo-2-methylphenyl)amine 284033-35-8P, 4-[4-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-4H-isoxazol-5-one 284033-36-9P, 4-[3,4-Difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-4H-isoxazol-5-one 284033-37-0P, 4-[3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)phenyl]-4H-isoxazol-5-one 284033-38-1P, 4-[5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl]-4H-isoxazol-5-one 284033-39-2P, 4-[4-Fluoro-2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]-4H-isoxazol-5-one 321595-39-5P, [4-Chloro-2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl]-(4-iodo-2-methylphenyl)amine

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of (2-heterocyclylphenyl)(4-iodophenyl)amines as MEK inhibitors for treatment of chronic pain)

IT 148553-50-8, Pregabalin 212631-61-3, PD 198306 212631-79-3, PD 184352 283602-39-1 284030-47-3, PD 254552 285125-85-1

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of (2-heterocyclylphenyl)(4-iodophenyl)amines as MEK inhibitors for treatment of chronic pain)

IT 142805-58-1, MEK kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(preparation of (2-heterocyclylphenyl)(4-iodophenyl)amines as MEK inhibitors for treatment of chronic pain)

IT 124-68-5, 2-Amino-2-methyl-1-propanol 3438-16-2, 5-Chloro-2-methoxybenzoic acid 10308-82-4, Aminoguanidine nitrate 13194-68-8, 4-Iodo-2-methylaniline 212628-45-0, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 284033-40-5, (2,3-Difluoro-6-cyanophenyl)-(4-iodo-2-methylphenyl)amine

RL: RCT (Reactant); RACT (Reactant or reagent)

(starting material; preparation of (2-heterocyclylphenyl)(4-iodophenyl)amines as MEK inhibitors for treatment of chronic pain)

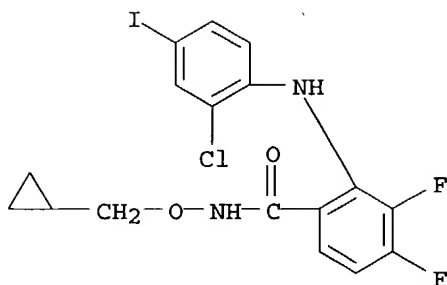
IT 212631-79-3, PD 184352

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of (2-heterocyclylphenyl)(4-iodophenyl)amines as MEK inhibitors for treatment of chronic pain)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 12 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:63817 HCAPLUS

DN 134:131530

ED Entered STN: 26 Jan 2001

TI Preparation of phenylaminobenzimidazoles and analogs as MEK inhibitors for the treatment of chronic pain

IN Barrett, Stephen Douglas; Bridges, Alexander James; Tecle, Haile; Dixon, Alistair; Lee, Kevin; Pinnock, Robert Denham

PA Warner-Lambert Company, USA

SO PCT Int. Appl., 88 pp.

CODEN: PIXXD2

DT Patent

LA English

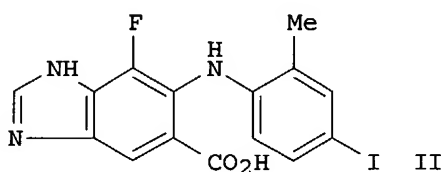
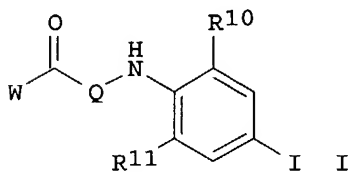
IC ICM A61K031-00

CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001005390	A2	20010125	WO 2000-US18345	20000705 <--
	WO 2001005390	A3	20010517		
	W:	AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	EP 1202731	A2	20020508	EP 2000-947013	20000705 <--
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL			
	ZA 2001009906	A	20030228	ZA 2001-9906	20011130 <--
PRAI	US 1999-144418P	P	19990716 <--		
	WO 2000-US18345	W	20000705 <--		
OS	MARPAT 134:131530				
GI					



AB The title compds. (I) [wherein W = OR1, NR2OR1, NRARB, NR2NRARB, O(CH2)2-4NRARB, or NR2(CH2)2-4NRARB; R1 = H, (phenyl)alkyl,

(phenyl)alkenyl, (phenyl)alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, or (CH<sub>2</sub>)<sub>2</sub>-4NRCRD; R<sub>2</sub> = H, (cyclo)alkyl, Ph, heterocyclyl, or cycloalkylmethyl; RA = H, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkynyl, cycloalkyl, Ph, heterocyclyl, heterocyclylalkyl, aminosulfonylphenyl(alkyl), aminosulfonyl(cyclo)alkyl, aminosulfonylcycloalkylalkyl, or (CH<sub>2</sub>)<sub>2</sub>-4NRCRD; RB, RC, and RD = independently H, (cyclo)alkyl, alkenyl, alkynyl, or Ph; or NRCRD = morpholinyl, piperizinyl, pyrrolidinyl, or piperidinyl; Q = a variety of (un)substituted benzo-fused heterocycles; R<sub>10</sub> and R<sub>11</sub> = independently H, Me, halo, or NO<sub>2</sub> were prepared for the treatment of chronic pain. For example, cycloaddn. of Me 4,5-diamino-3-fluoro-2-(2-methylphenylamino)benzoate (5-step preparation given) with formic acid gave Me 7-fluoro-6-(2-methylphenylamino)-1H-benzimidazole-5-carboxylate (87%). Iodination using benzyltrimethylammonium dichloriodinate and ZnCl<sub>2</sub> in AcOH (68%) and deesterification using potassium trimethylsilanolate in THF afforded PD 205293 (II) in 9% yield. II displayed an APK IC<sub>50</sub> of 14 nM and an IC<sub>50</sub> ≥ 10 μM against colon 26 cells. Biol. assays indicated that MEK inhibitors exert an antiallodynic effect in CCI-induced neuropathic rats when administered intrathecally and that the antiallodynic effect correlates with the affinity of the compds.

ST phenylamino benzimidazole prepn mek inhibitor; benzimidazole prepn  
analgesic; benzo fused heterocycle prepn chronic pain treatment

IT Pain  
Skin, disease  
(allodynia, treatment; preparation of phenylaminobenzimidazoles and analogs as MEK inhibitors for treatment of chronic pain)

IT Vitamins  
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)  
(avitaminosis, treatment of pain associated with; preparation of phenylaminobenzimidazoles and analogs as MEK inhibitors for treatment of chronic pain)

IT Kidney, disease  
(failure, treatment of pain associated with; preparation of phenylaminobenzimidazoles and analogs as MEK inhibitors for treatment of chronic pain)

IT Analgesics  
(preparation of phenylaminobenzimidazoles and analogs as MEK inhibitors for treatment of chronic pain)

IT Pain  
(treatment of idiopathic and post-operative; preparation of phenylaminobenzimidazoles and analogs as MEK inhibitors for treatment of chronic pain)

IT Alcoholism  
Arthritis  
Hypothyroidism  
Inflammation  
(treatment of pain associated with; preparation of phenylaminobenzimidazoles and analogs as MEK inhibitors for treatment of chronic pain)

IT 74124-04-2P, Cyclopropylmethoxylamine hydrochloride 113211-15-7P,  
2-Cyclopropylmethoxyisindole-1,3-dione 197520-71-1P,  
5-Nitro-2,3,4-trifluorobenzoic acid 284030-57-5P, 4-Amino-2,3-difluoro-5-nitrobenzoic acid 284030-58-6P, Methyl 4-amino-2,3-difluoro-5-nitrobenzoate 284030-59-7P, Methyl 4-amino-3-fluoro-2-(2-methylphenylamino)-5-nitrobenzoate 284030-60-0P, Methyl 4,5-diamino-3-fluoro-2-(2-methylphenylamino)benzoate 284030-61-1P, Methyl 7-fluoro-6-(2-methylphenylamino)-1H-benzimidazole-5-carboxylate 284030-62-2P, Methyl 7-fluoro-6-(4-iodo-2-methylphenylamino)-1H-benzimidazole-5-carboxylate 284030-63-3P, 2,3-Difluoro-4-hydroxy-5-nitrobenzoic acid 284030-64-4P, Methyl 2,3-difluoro-4-hydroxy-5-nitrobenzoate

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)

(intermediate; preparation of phenylaminobenzimidazoles and analogs as MEK inhibitors for treatment of chronic pain)

IT 284486-99-3P, 7-Fluoro-6-(4-iodo-2-methylphenylamino)-1H-benzimidazole-5-carboxylic acid pentafluorophenyl ester

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of phenylaminobenzimidazoles and analogs as MEK inhibitors for treatment of chronic pain)

IT 284030-28-0P, 7-Fluoro-6-(4-iodo-2-methylphenylamino)benzoxazole-5-carboxylic acid 284030-29-1P, 7-Fluoro-6-(4-iodo-2-methylphenylamino)benzothiazole-5-carboxylic acid 284030-30-4P, 7-Fluoro-6-(4-iodo-2-methylphenylamino)benzo[1,2,5]thiadiazole-5-carboxylic acid 284030-31-5P, 7-Fluoro-6-(4-iodo-2-methylphenylamino)benzo[1,2,5]oxadiazole-5-carboxylic acid 284030-32-6P, 7-Fluoro-6-(4-iodo-2-methylphenylamino)-2-(2-hydroxyethyl)-1H-benzimidazole-5-carboxylic acid 284030-33-7P, 7-Fluoro-6-(4-iodo-2-methylphenylamino)-2-(2-dimethylaminoethyl)-1H-benzimidazole-5-carboxylic acid 284030-34-8P, 7-Fluoro-6-(4-iodo-2-methylphenylamino)-1-acetylbenzimidazole-5-carboxylic acid 284030-35-9P, 8-Fluoro-7-(4-iodo-2-methylphenylamino)quinoxaline-6-carboxylic acid 284030-36-0P, 7-Fluoro-6-(4-iodo-2-methylphenylamino)-1H-benzotriazole-5-carboxylic acid 284030-47-3P, 7-Fluoro-6-(4-iodo-2-methylphenylamino)-1H-benzimidazole-5-carboxylic acid cyclopropylmethoxyamide 284486-91-5P, 7-Fluoro-6-(4-iodo-2-methylphenylamino)-1H-benzimidazole-5-carboxylic acid 321655-20-3P, 7-Fluoro-6-(4-iodo-2-methylphenylamino)-6,7-dihydro-1H-benzimidazole-5-carboxylic acid hydrochloride 321655-21-4P, 7-Fluoro-6-(4-iodo-2-methylphenylamino)-3H-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)amide 321655-22-5P, 6-(2-Chloro-4-iodophenylamino)-7-fluoro-1H-benzimidazole-5-carboxylic acid

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of phenylaminobenzimidazoles and analogs as MEK inhibitors for treatment of chronic pain)

IT 148553-50-8, Pregabalin 212631-61-3, PD 198306 212631-79-3, PD 184352 283602-39-1 285125-85-1

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of phenylaminobenzimidazoles and analogs as MEK inhibitors for treatment of chronic pain)

IT 142805-58-1, MEK kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(preparation of phenylaminobenzimidazoles and analogs as MEK inhibitors for treatment of chronic pain)

IT 95-53-4, o-Toluidine, reactions 524-38-9, N-Hydroxyphthalimide 2516-33-8, Cyclopropanemethanol 61079-72-9, 2,3,4-Trifluorobenzoic acid

RL: RCT (Reactant); RACT (Reactant or reagent)

(starting material; preparation of phenylaminobenzimidazoles and analogs as MEK inhibitors for treatment of chronic pain)

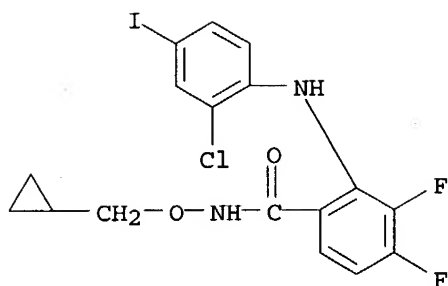
IT 212631-79-3, PD 184352

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of phenylaminobenzimidazoles and analogs as MEK inhibitors for treatment of chronic pain)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 13 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN  
 AN 2000:805039 HCAPLUS  
 DN 133:344610  
 ED Entered STN: 15 Nov 2000  
 TI Specific inhibition of the p42/44 mitogen-activated protein kinase cascade sensitizes tumor cells  
 IN Dent, Paul; Grant, Steven; Jarvis, W. David  
 PA Virginia Commonwealth University, USA  
 SO U.S., 19 pp.  
 CODEN: USXXAM  
 DT Patent  
 LA English  
 IC A01N043-02; A61K031-335  
 NCL 514449000  
 CC 1-6 (Pharmacology)  
 Section cross-reference(s): 7, 8

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6147107	A	20001114	US 1998-203342	19981220 <--
PRAI	US 1998-203342		19981220	<--	

AB Mammalian cancer cells are effectively killed when treated with a lethal agent (e.g. radiation or chemotherapeutic agents) in combination with an inhibitor specific for the p42/44 mitogen-activated protein (MAP) kinase cascade "proper". Inhibition of the p42/44 MAP kinase cascade with an agent such as PD184352 inhibits the ability of Raf protein kinases to phosphorylate and activate the enzymes MEK1 and MEK2. This in turn potentiates the apoptotic activity of radiation and the chemotherapeutic agents ara-C and taxol.

ST tumor sensitization MAP kinase cascade inhibition

IT Temperature effects, biological  
 (heat, sensitization to; specific inhibition of the p42/44 mitogen-activated protein kinase cascade sensitizes tumor cells)

IT Radiosensitizers, biological  
 (pharmaceutical; specific inhibition of the p42/44 mitogen-activated protein kinase cascade sensitizes tumor cells)

IT Light  
 (red, sensitization to high-intensity; specific inhibition of the p42/44 mitogen-activated protein kinase cascade sensitizes tumor cells)

IT Electric field  
 IR radiation  
 Magnetic field  
 UV radiation  
 (sensitization to; specific inhibition of the p42/44 mitogen-activated protein kinase cascade sensitizes tumor cells)

IT Antitumor agents  
 Light sensitization  
 (specific inhibition of the p42/44 mitogen-activated protein kinase

cascade sensitizes tumor cells)

IT Taxanes  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (specific inhibition of the p42/44 mitogen-activated protein kinase cascade sensitizes tumor cells)

IT 137632-07-6, P44 MAP kinase 137632-08-7, P42 MAP kinase 139691-76-2, RAF kinase 142805-58-1 150316-14-6, MEK2 protein kinase  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (specific inhibition of the p42/44 mitogen-activated protein kinase cascade sensitizes tumor cells)

IT 147-94-4, Ara-C 33069-62-4, Taxol 109511-58-2, U0126 167869-21-8, PD 98059 212631-79-3, PD 184352 305350-87-2, SL 327 305350-88-3, SW 073  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (specific inhibition of the p42/44 mitogen-activated protein kinase cascade sensitizes tumor cells)

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD

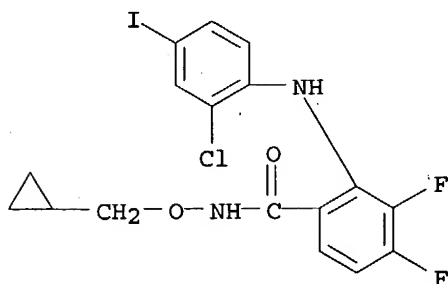
RE

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IT 212631-79-3, PD 184352  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (specific inhibition of the p42/44 mitogen-activated protein kinase cascade sensitizes tumor cells)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 14 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2000:771648 HCAPLUS

DN 134:67957

ED Entered STN: 03 Nov 2000

TI Specificity and mechanism of action of some commonly used protein kinase inhibitors

AU Davies, Stephen P.; Reddy, Helen; Caivano, Matilde; Cohen, Philip

CS Division of Signal Transduction Therapy, University of Dundee, Dundee, DD1 5EH, UK

SO Biochemical Journal (2000), 351(1), 95-105  
 CODEN: BIJOAK; ISSN: 0264-6021

PB Portland Press Ltd.

DT Journal

LA English

CC 7-3 (Enzymes)

Section cross-reference(s): 1

AB The specificities of 28 com. available compds. reported to be relatively selective inhibitors of particular serine/threonine-specific protein kinases have been examined against a large panel of protein kinases. The compds. KT 5720, Rottlerin and quercetin were found to inhibit many protein kinases, sometimes much more potently than their presumed targets, and conclusions drawn from their use in cell-based expts. are likely to be erroneous. Ro 318220 and related bisindolmaleimides, as well as H89, HA1077 and Y 27632, were more selective inhibitors, but still inhibited two or more protein kinases with similar potency. LY 294002 was found to inhibit casein kinase-2 with similar potency to phosphoinositide (phosphatidylinositol) 3-kinase. The compds. with the most impressive selectivity profiles were KN62, PD 98059, U0126, PD 184352, rapamycin, wortmannin, SB 203580 and SB 202190. U0126 and PD 184352, like PD 98059, were found to block the mitogen-activated protein kinase (MAPK) cascade in cell-based assays by preventing the activation of MAPK kinase (MKK1), and not by inhibiting MKK1 activity directly. Apart from rapamycin and PD 184352, even the most selective inhibitors affected at least one addnl. protein kinase. Our results demonstrate that the specificities of protein kinase inhibitors cannot be assessed simply by studying their effect on kinases that are closely related in primary structure. The authors propose guidelines for the use of protein kinase inhibitors in cell-based assays.

ST protein kinase inhibitor mechanism specificity

IT 52660-18-1

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(2; specificity and mechanism of action of commonly used protein kinase inhibitors)

IT 9059-09-0

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(3β; specificity and mechanism of action of commonly used protein kinase inhibitors)

IT 141467-21-2

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(II; specificity and mechanism of action of commonly used protein kinase inhibitors)

IT 192230-91-4, MKK4 kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(MKK3 and MKK4 and MKK7; specificity and mechanism of action of commonly used protein kinase inhibitors)

IT 90698-26-3, MAPKAP kinase 1

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(isoform b; specificity and mechanism of action of commonly used protein kinase inhibitors)

IT 148640-14-6, Protein kinase B

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(isoform α; specificity and mechanism of action of commonly used protein kinase inhibitors)

IT 82-08-6, Rottlerin 117-39-5, Quercetin 2804-16-2, 10-[3-(1-Piperazinyl)propyl]-2-trifluoromethyl-phenothiazine 7439-93-2, Lithium, biological studies 7447-41-8, Lithium chloride, biological studies 19545-26-7, Wortmannin 34316-15-9, Chelerythrine 53123-88-9, Rapamycin 85753-43-1, K252c 103745-39-7, HA1077 108068-98-0, KT 5720

109511-58-2, U0126 112953-11-4, UCN1 125314-64-9, Ro 31-8220  
 127191-97-3, KN62 127243-85-0, H89 136194-77-9, Go6976 146986-50-7,  
 Y 27632 152121-30-7, SB 202190 152121-47-6, SB 203580 154447-36-6,  
 LY 294002 167869-21-8, PD 98059 212631-79-3, PD 184352

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(specificity and mechanism of action of commonly used protein kinase inhibitors)

IT 9001-88-1, Phosphorylase kinase 9026-43-1, Protein kinase 51845-53-5, Myosin light chain kinase 115926-52-8, Phosphoinositide 3-kinase 137632-08-7, ERK2 kinase 142008-29-5, CAMP-dependent protein kinase 142243-02-5, Mitogen-activated protein kinase 146838-30-4 154907-65-0, Checkpoint kinase 156621-09-9, Mitogen-and stress-activated protein kinase-1 165245-96-5, Stress-activated protein kinase 2a 172522-01-9, AMP-activated protein kinase 176023-64-6, SAPK3 kinase 178037-70-2, Serum/glucocorticoid-inducible protein kinase 179800-23-8, Stress-activated protein kinase 2b 182938-08-5, Protein kinase ROCK-II 185156-08-5, Protein kinase C-related kinase-2 191808-15-8, 3-Phosphoinositide-dependent protein kinase 1 192333-55-4, SAPK4 kinase 194739-73-6, MKK6 kinase 197664-51-0, Lymphocyte-oriented protein kinase 212378-03-5, Protein kinase PRAK 244634-79-5, Kinase (phosphorylating), gene chk2 protein

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(specificity and mechanism of action of commonly used protein kinase inhibitors)

IT 141436-78-4

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

( $\alpha$ ,  $\alpha$  and  $\delta$ ; specificity and mechanism of action of commonly used protein kinase inhibitors)

IT 289898-51-7, JNK1 protein kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

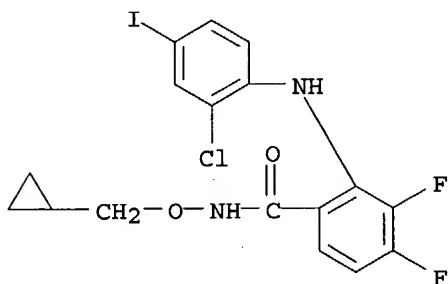
( $\alpha$ 1; specificity and mechanism of action of commonly used protein kinase inhibitors)

RE.CNT 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD

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- IT 212631-79-3, PD 184352  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)  
 (specificity and mechanism of action of commonly used protein kinase inhibitors)
- RN 212631-79-3 HCAPLUS  
 CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)

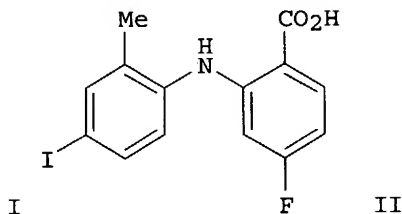
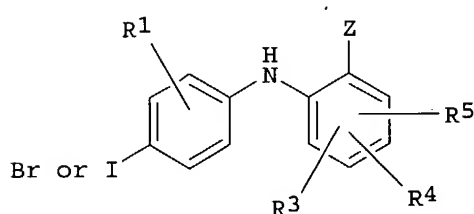


- L112 ANSWER 15 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN  
 AN 2000:475534 HCAPLUS  
 DN 133:89333  
 ED Entered STN: 14 Jul 2000  
 TI Preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivatives as MEK inhibitors for use as antiviral agents  
 IN Bridges, Alexander James; Dudley, David Thomas; Gracheck, Stephen Joseph; Meyer, Annette Lynn; Saltiel, Alan Robert; Sebolt-Leopold, Judith

PA Warner-Lambert Company, USA  
 SO PCT Int. Appl., 112 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 IC ICM A61K031-35  
 ICS A61K031-165; A61P031-12; A61P031-18; A61P031-22  
 CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)  
 Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000040237	A1	20000713	WO 1999-US30484	19991221 <--
	W:	AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	CA 2358438	AA	20000713	CA 1999-2358438	19991221 <--
	EP 1140067	A1	20011010	EP 1999-966522	19991221 <--
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
	ZA 2001004000	A	20020816	ZA 2001-4000	20010516 <--
PRAI	US 1999-115026P	P	19990107 <--		
	WO 1999-US30484	W	19991221 <--		
OS	MARPAT 133:89333				
GI					



AB The title compds. (I) [wherein R1 = H, OH, alkyl, alkoxy, halo, CF3, or CN; R3-R5 = independently H, OH, halo, CF3, alkyl, alkoxy, NO2, CN, or (O or NH)m-(CH2)n-R9, where R9 = H, OH, CO2H, or NR10R11; m = 0 or 1; n = 0-4; R10 and R11 = H, alkyl, or taken together with the N to which they are attached form a 3-10 membered ring; Z = CO2R7, tetrazolyl, CONR6R7, CONHNR10R11, or CH2OR7; R6 and R7 = independently H, (cyclo)alkyl, alkenyl, alkynyl, acyl, (hetero)aryl, or taken together with the N to which they are attached form a 3-10 membered ring, etc.] were prepared by standard or combinatorial synthetic methods involving the addition of halobenzoic

acids to haloanilines and optional reduction or amidation of the acid. For example, treatment of 2-amino-5-iodotoluene in THF with LDA in THF/heptane/ethenylbenzene solution, followed by addition of

2,4-difluorobenzoic

acid in THF afforded II. In assays evaluating the ability to prevent and inhibit growth of human cytomegalovirus (HCMV) and herpesvirus (HSV-1), 2-(2-methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-bromobenzamide (PD 177168) gave IC50 of 0.8  $\mu$ M and 3.0  $\mu$ M, resp., with TC50 of 9  $\mu$ M and 11  $\mu$ M, resp. PD 177168 also showed anti-HIV

- activity with EC50 of 0.18  $\mu$ M and TC50 of 5.95  $\mu$ M. Thus, I are potent MEK inhibitors that are useful in the prevention and treatment of viral infections, especially HIV, hepatitis B, and herpesvirus.
- ST diphenylamine std combinatorial prepn MEK inhibitor; bromophenylamino iodophenylamino benzamide prepn antiviral; benzamide prepn HIV hepatitis B herpes virus treatment
- IT Hepatitis  
(B, treatment; preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors that are useful in the prevention and treatment of viral infections, especially HIV, hepatitis B, and herpesvirus)
- IT Combinatorial library  
Solid phase synthesis  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of acid)
- IT Anti-AIDS agents  
Antiviral agents  
Human immunodeficiency virus 1  
Toxicity  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors that are useful in the prevention and treatment of viral infections, especially HIV, hepatitis B, and herpesvirus)
- IT Cytomegalovirus  
(treatment; preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors that are useful in the prevention and treatment of viral infections, especially HIV, hepatitis B, and herpesvirus)
- IT 282104-12-5, PD 178390  
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(control compound; preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of acid)
- IT 167869-21-8P, PD 098059 212630-41-6P, PD 170611 212630-94-9P, 5-Bromo-N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212631-57-7P, PD 185848 212631-61-3P, PD 198306 212631-67-9P, PD 184161 212631-78-2P, PD 203311 219778-04-8P, PD 185625 219778-52-6P, PD 180841  
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of acid)
- IT 282103-63-3, PD 177098  
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of acid)
- IT 212628-43-8P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-46-1P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-48-3P, 5-Chloro-2-(4-iodo-2-methylphenylamino)benzoic acid  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of acid)
- IT 212628-44-9P, 3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)benzoic acid

212628-45-0P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-47-2P, 5-Chloro-2-(2-chloro-4-iodophenylamino)benzoic acid  
212628-49-4P, Sodium 5-Chloro-2-(4-iodo-2-methylphenylamino)benzoate  
212628-50-7P, 5-Bromo-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-51-8P, 2-(2-Chloro-4-iodophenylamino)-5-nitrobenzoic acid  
212628-52-9P 212628-53-0P, 2-(4-Iodo-2-methylphenylamino)-5-nitrobenzoic acid  
212628-54-1P, 2-(2-Fluoro-4-iodophenylamino)-5-nitrobenzoic acid  
212628-55-2P, 2-(4-Bromo-2-methylphenylamino)-4-fluorobenzoic acid  
212628-56-3P, 2-(2-Bromo-4-iodophenylamino)-5-nitrobenzoic acid  
212628-57-4P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluorobenzoic acid  
212628-58-5P, 3-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-59-6P, 3,4-Difluoro-2-(4-iodo-2-methoxyphenylamino)benzoic acid  
212628-60-9P, 4-Chloro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-61-0P, 2-(4-Iodo-2-methylphenylamino)benzoic acid 212628-62-1P,  
5-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-63-2P,  
5-Iodo-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-65-4P,  
2,3,5-Trifluoro-4-(4-iodo-2-methylphenylamino)benzoic acid 212628-67-6P  
212628-69-8P, 2-(4-Iodophenylamino)-5-methoxybenzoic acid 212628-71-2P,  
3-Chloro-2-(2-chloro-4-iodophenylamino)benzoic acid 212628-72-3P,  
2-Fluoro-6-(4-iodo-2-methylphenylamino)benzoic acid 212628-73-4P  
212628-74-5P, 5-Methyl-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-75-6P, 2-Chloro-6-(4-iodo-2-methylphenylamino)benzoic acid  
212628-76-7P, 2-(4-Iodo-2-methylphenylamino)-4-nitrobenzoic acid  
212628-77-8P, 5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212628-78-9P 212628-79-0P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212628-80-3P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-methylbenzamide 212628-81-4P,  
N-Ethyl-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212628-82-5P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)-N,N-dimethylbenzamide  
212628-83-6P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(1H-tetrazol-5-yl)-benzamide 212628-84-7P, 5-Bromo-2-(4-iodo-2-methylphenylamino)benzamide  
212628-85-8P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N,N-dimethylbenzamide 212628-86-9P, [[5-Chloro-2-(4-iodo-2-methylphenylamino)benzoyl]amino]acetic acid 212628-87-0P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-propylbenzamide 212628-88-1P,  
5-Bromo-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide  
212628-89-2P, N,N-Diethyl-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide  
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[5-Chloro-2-(4-iodo-2-methylphenylamino)phenyl]methanol 212628-97-2P,  
[2-(4-Iodo-2-methylphenylamino)-5-nitrophenyl]methanol 212628-98-3P,  
[5-Bromo-2-(4-iodo-2-methylphenylamino)phenyl]methanol 212628-99-4P,  
5-Bromo-3,4-difluoro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-00-0P, N-(2,3-Dihydroxypropyl)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-01-1P,  
5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-02-2P, 3,4-Difluoro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-03-3P, N-(2,3-Dihydroxypropyl)-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-04-4P,  
3,4-Difluoro-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide  
212629-05-5P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-06-6P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyridin-4-ylethyl)benzamide 212629-07-7P,  
4-Fluoro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide  
212629-08-8P, 5-Bromo-N-(3-dimethylaminopropyl)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-09-9P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-10-2P,  
3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-11-3P, 3,4-Difluoro-2-(4-iodo-2-

methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-12-4P,  
3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyridin-4-  
ylethyl)benzamide 212629-13-5P, N-(3-Dimethylaminopropyl)-3,4-difluoro-2-  
(4-iodo-2-methylphenylamino)benzamide 212629-14-6P, N-Benzyl-4-fluoro-2-  
(4-iodo-2-methylphenylamino)benzamide 212629-15-7P, 2-(4-Bromo-2-  
methylphenylamino)-3,4-difluoro-N-(2-hydroxyethyl)benzamide  
212629-16-8P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-  
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N-(3-piperidin-1-ylpropyl)benzamide 212629-18-0P, 3,4-Difluoro-2-(4-iodo-  
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4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-thiophen-2-ylethyl)benzamide  
212629-20-4P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-  
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methylphenylamino)benzamide 212629-36-2P, 5-Fluoro-N-[3-[4-(2-  
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5-nitro-N-pyridin-4-ylmethylbenzamide 212629-38-4P, 5-Bromo-N-[3-[4-(2-  
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5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide  
212629-41-9P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-  
ylethyl)benzamide 212629-42-0P, 5-Bromo-N-(2-diethylaminoethyl)-2-(4-  
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212629-44-2P, N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-5-bromo-2-(4-iodo-2-  
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212629-50-0P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-  
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212629-62-4P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-  
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methylphenylamino)benzamide 212629-66-8P, 5-Bromo-2-(4-iodo-2-

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N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-2-(4-iodo-2-methylphenylamino)-5-  
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212629-73-7P, 5-Chloro-N-(2-diisopropylaminoethyl)-2-(4-iodo-2-  
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N-(3-piperidin-1-ylpropyl)benzamide 212629-90-8P, N-[3-(N,N-  
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N-(2-Diisopropylaminoethyl)-5-fluoro-2-(4-iodo-2-  
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methylphenylamino)thiobenzoic acid S-phenethyl ester 212629-95-3P,  
5-Chloro-2-(4-iodo-2-methylphenylamino)thiobenzoic acid S-phenethyl ester  
212629-98-6P 212629-99-7P 212630-00-7P, N-Cyclopropyl-5-fluoro-2-(4-  
iodo-2-methylphenylamino)benzamide 212630-03-0P, 5-Fluoro-N-(2-  
hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212630-04-1P,  
N-Benzyloxy-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide  
212630-05-2P, N-Benzyloxy-5-bromo-2-(4-iodo-2-methylphenylamino)benzamide  
212630-06-3P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-(4-  
sulfamoylbenzyl)benzamide 212630-07-4P, N-(2-Hydroxyethyl)-5-iodo-2-(4-  
iodo-2-methylphenylamino)benzamide 212630-08-5P, N-(2-Hydroxyethyl)-2-(4-  
iodo-2-methylphenylamino)-5-nitrobenzamide 212630-09-6P,  
2-(4-Iodo-2-methylphenylamino)-N-methyl-5-nitro-N-phenylbenzamide  
212630-10-9P, 5-Chloro-N-cyclopropyl-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-11-0P, 5-Fluoro-2-(4-iodo-2-  
methylphenylamino)-N-methyl-N-phenylbenzamide 212630-12-1P,  
N-Allyl-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-13-2P,  
N-Benzyloxy-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-14-3P,  
5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(4-sulfamoylbenzyl)benzamide  
212630-15-4P, N-Allyl-5-chloro-2-(4-iodo-2-methylphenylamino)benzamide  
212630-16-5P, N-Cyclopropyl-2-(4-iodo-2-methylphenylamino)-5-  
nitrobenzamide 212630-17-6P, 5-Bromo-N-cyclopropyl-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-18-7P, 5-Chloro-2-(4-iodo-2-  
methylphenylamino)-N-methyl-N-phenylbenzamide 212630-19-8P,  
5-Iodo-2-(4-iodo-2-methylphenylamino)-N-(4-sulfamoylbenzyl)benzamide  
212630-20-1P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(4-  
sulfamoylbenzyl)benzamide 212630-21-2P, N-Allyl-2-(4-iodo-2-  
methylphenylamino)-5-nitrobenzamide 212630-22-3P, N-Allyl-5-bromo-2-(4-  
iodo-2-methylphenylamino)benzamide 212630-23-4P, 5-Fluoro-2-(4-iodo-2-  
methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-24-5P,  
N-Cyclopropyl-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide  
212630-25-6P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-methyl-N-  
phenylbenzamide 212630-26-7P, N-Benzyloxy-2-(4-iodo-2-methylphenylamino)-  
5-nitrobenzamide 212630-27-8P, N-Cyclohexyl-5-iodo-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-28-9P, N-Allyl-5-iodo-2-(4-iodo-2-

methylphenylamino)benzamide 212630-29-0P, 5-Iodo-2-(4-iodo-2-methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-30-3P, 2-(4-Iodo-2-methylphenylamino)-N-(3-methylbenzyl)-5-nitrobenzamide 212630-31-4P, 5-Iodo-2-(4-iodo-2-methylphenylamino)-N-methyl-N-phenylbenzamide 212630-32-5P, N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-33-6P, 5-Chloro-N-cyclohexyl-2-(4-iodo-2-methylphenylamino)benzamide 212630-34-7P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-35-8P, 5-Bromo-N-cyclohexyl-2-(4-iodo-2-methylphenylamino)benzamide 212630-36-9P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-37-0P, N-Cyclohexyl-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-38-1P 212630-39-2P, (4-Iodo-2-methylphenyl)-[2-(1H-tetrazol-5-yl)phenyl]amine 212630-42-7P, PD 171984 212630-43-8P, 2-(4-Bromo-2-methylphenylamino)-4-fluoro-N-hydroxybenzamide 212630-44-9P, 5-Chloro-N-hydroxy-2-(4-iodo-2-methylphenylamino)-N-methylbenzamide 212630-45-0P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(terahdropyran-2-yloxy)benzamide 212630-46-1P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-methoxybenzamide 212630-47-2P, 4-Fluoro-N-hydroxy-2-(4-fluoro-2-methylphenylamino)benzamide 212630-48-3P, 4-Fluoro-N-hydroxy-2-(2-methylphenylamino)benzamide 212630-49-4P, 4-Fluoro-2-(4-fluoro-2-methylphenylamino)-N-(tetrahydropyran-2-yloxy)benzamide 212630-50-7P, 4-Fluoro-N-hydroxy-2-(4-chloro-2-methylphenylamino)benzamide 212630-51-8P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-phenylmethoxybenzamide 212630-52-9P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-methoxybenzamide 212630-53-0P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-methoxybenzamide 212630-54-1P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-methoxybenzamide 212630-55-2P, 2-(4-Bromo-2-methylphenylamino)-N-ethoxy-3,4-difluorobenzamide 212630-56-3P, 5-Bromo-N-ethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-57-4P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-isopropoxybenzamide 212630-58-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-isopropoxybenzamide 212630-59-6P, 4-Fluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 212630-60-9P, 3,4-Difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 212630-61-0P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(furan-3-ylmethoxy)benzamide 212630-62-1P, 5-Bromo-3,4-difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 212630-63-2P, 5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-64-3P 212630-65-4P 212630-66-5P 212630-67-6P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(1-methyl-2-propyn-1-yloxy)benzamide 212630-68-7P 212630-69-8P 212630-70-1P 212630-71-2P 212630-72-3P 212630-73-4P 212630-74-5P 212630-75-6P 212630-76-7P 212630-77-8P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(3-methyl-5-phenylpent-2-en-4-ynyloxy)benzamide 212630-78-9P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(3-methyl-5-phenylpent-2-en-4-ynyloxy)benzamide 212630-79-0P, N-Ethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-80-3P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-propoxybenzamide 212630-81-4P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-propoxybenzamide 212630-82-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-propoxybenzamide 212630-83-6P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-propoxybenzamide 212630-84-7P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-isopropoxybenzamide 212630-85-8P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-isopropoxybenzamide 212630-86-9P, N-Cyclobutyloxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-87-0P, 2-(4-Bromo-2-methylphenylamino)-N-cyclobutyloxy-3,4-difluorobenzamide 212630-88-1P, N-Cyclopentyloxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-89-2P, 2-(4-Bromo-2-methylphenylamino)-N-cyclopentyloxy-3,4-difluorobenzamide 212630-90-5P, N-Cyclopropylmethoxy-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-92-7P, 2-(4-Bromo-2-methylphenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide 212630-96-1P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-

N-(2-phenoxyethoxy)benzamide 212630-98-3P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-phenoxyethoxy)benzamide 212630-99-4P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-phenoxyethoxy)benzamide 212631-00-0P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(thiophen-2-ylmethoxy)benzamide 212631-01-1P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(thiophen-2-ylmethoxy)benzamide 212631-02-2P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(thiophen-2-ylmethoxy)benzamide 212631-03-3P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-methylallyloxy)benzamide 212631-04-4P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-methylallyloxy)benzamide 212631-05-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-methylallyloxy)benzamide 212631-06-6P, N-(But-2-enyloxy)-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212631-07-7P, N-(But-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212631-08-8P, 2-(4-Bromo-2-methylphenylamino)-N-(but-2-enyloxy)-3,4-difluorobenzamide  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of acid)

IT 212631-09-9P 212631-13-5P 212631-15-7P, N-Cyclopentyloxy-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212631-28-2P 212631-29-3P  
 212631-33-9P 212631-35-1P 212631-36-2P, 5-Chloro-N-hydroxy-2-(4-iodo-2-methylphenylamino)benzamide 212631-37-3P 212631-38-4P 212631-39-5P  
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 212631-45-3P 212631-46-4P, PD 184386 212631-47-5P 212631-48-6P  
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 212631-60-2P 212631-62-4P, PD 298127 212631-63-5P 212631-64-6P  
 212631-65-7P 212631-66-8P 212631-68-0P 212631-69-1P 212631-70-4P, PD 297189 212631-71-5P 212631-72-6P 212631-73-7P 212631-74-8P  
 212631-75-9P 212631-76-0P 212631-77-1P 212631-79-3P, PD 184352 212631-80-6P 212631-81-7P 219777-46-5P, N-(3-tert-Butylpropyn-2-yl)oxy-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 219777-60-3P, PD 188563 219794-13-5P 219794-21-5P, 2-(4-Iodo-2-methylphenylamino)-5-nitrothiobenzoic acid S-benzyl ester 277315-06-7P, (3-Hydroxypyrrolidin-1-yl)-[2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]methanone 277315-07-8P, [5-Bromo-2-(4-iodo-2-methylphenylamino)phenyl]-(3-hydroxypyrrolidin-1-yl)-methanone 277315-08-9P, [5-Chloro-2-(4-iodo-2-methylphenylamino)phenyl]-(3-hydroxypyrrolidin-1-yl)-methanone 277315-09-0P, [5-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-(3-hydroxypyrrolidin-1-yl)-methanone 277315-10-3P 277315-12-5P 277335-43-0P 278609-85-1P, PD 297190 278609-99-7P, PD 296711 278610-42-7P, PD 296770 278610-51-8P, PD 296767

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of acid)

IT 352-33-0, 1-Chloro-4-fluorobenzene 1583-58-0, 2,4-Difluorobenzoic acid 6723-30-4, O-(Tetrahydro-2H-pyran-2-yl)-hydroxylamine 176317-02-5, 1-Bromo-2,3,4-trifluorobenzene

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of acid)

IT 13194-68-8P, 2-Amino-5-iodotoluene 57381-34-7P, 5-Chloro-2-fluorobenzonitrile 96515-79-6P, 5-Chloro-2-fluorobenzaldehyde 212631-82-8P, 5-Chloro-2-fluorobenzaldehyde oxime 212631-83-9P, 5-(5-Chloro-2-fluorophenyl)-1H-tetrazole 212631-84-0P 212631-85-1P, 5-Bromo-2,3,4-trifluorobenzoic acid 212631-86-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of acid)

IT 142805-58-1

RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors that are useful in the prevention and treatment of viral infections, especially HIV, hepatitis B, and herpesvirus)

IT 11028-71-0, Human herpesvirus 1

RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)  
(treatment; preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors that are useful in the prevention and treatment of viral infections, especially HIV, hepatitis B, and herpesvirus)

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

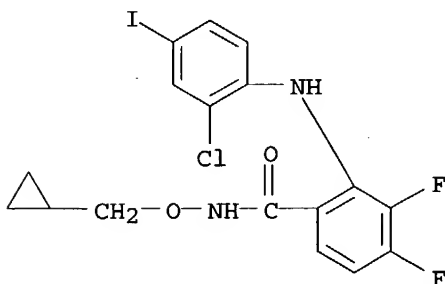
- (1) Doherty, A; WO 9901421 A 1999 HCAPLUS
- (2) Doherty, A; WO 9901426 A 1999 HCAPLUS
- (3) Gibellini, D; JOURNAL OF IMMUNOLOGY 1998, V160(8), P3891 HCAPLUS
- (4) Rodems, S; JOURNAL OF VIROLOGY 1998, V72(11), P9173 HCAPLUS
- (5) Schang, L; JOURNAL OF VIROLOGY 1998, V72(7), P5626 HCAPLUS
- (6) Shibutani, T; JOURNAL OF CLINICAL INVESTIGATION 1997, V100(8), P2054 HCAPLUS
- (7) Univ New York; WO 9857175 A 1998 HCAPLUS

IT 212631-79-3P, PD 184352

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of acid)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 16 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2000:475533 HCAPLUS

DN 133:89332

ED Entered STN: 14 Jul 2000

TI Preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivatives as MEK inhibitors for the treatment of asthma

IN Bridges, Alexander James; Dudley, David Thomas; Mobley, James Leslie; Saltiel, Alan Robert

PA Warner-Lambert Company, USA

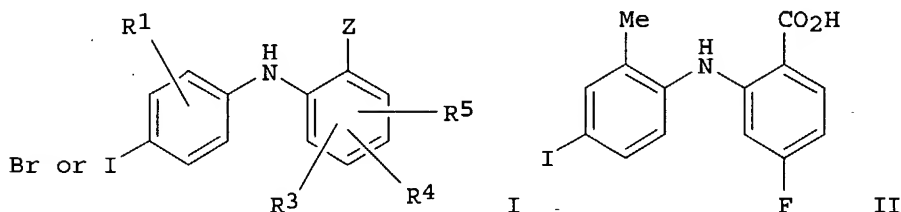
SO PCT Int. Appl., 106 pp.

CODEN: PIXXD2

DT Patent  
 LA English  
 IC ICM A61K031-195  
 CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)  
 Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000040235	A2	20000713	WO 1999-US30419	19991221 <--
	WO 2000040235	A3	20001109		
	W:	AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	EP 1140062	A2	20011010	EP 1999-968153	19991221 <--
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
	BR 9916785	A	20011023	BR 1999-16785	19991221 <--
	US 6696440	B1	20040224	US 2001-889091	20010711 <--
PRAI	US 1999-115086P	P	19990107 <--		
	WO 1999-US30419	W	19991221 <--		
OS	MARPAT 133:89332				
GI					



AB The title compds. (I) [wherein R1 = H, OH, alkyl, alkoxy, halo, CF3, or CN; R3-R5 = independently H, OH, halo, CF3, alkyl, alkoxy, NO2, CN, or (O or NH)m-(CH2)n-R9, where R9 = H, OH, CO2H, or NR10R11; m = 0 or 1; n = 0-4; R10 and R11 = H, alkyl, or taken together with the N to which they are attached form a 3-10 membered ring; Z = CO2R7, tetrazolyl, CONR6R7, CONHNR10R11, or CH2OR7; R6 and R7 = independently H, (cyclo)alkyl, alkenyl, alkynyl, acyl, (hetero)aryl, or taken together with the N to which they are attached form a 3-10 membered ring, etc.] were prepared by standard or combinatorial synthetic methods involving the addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid. For example, treatment of 2-amino-5-iodotoluene in THF with LDA in THF/heptane/ethenylbenzene solution, followed by addition of 2,4-difluorobenzoic acid in THF afforded II. In an in vitro assay, 2-(2-methyl-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide (PD 171984) prevented antigen-induced production of interleukin 5 (IL-5) by OVA-primed splenocytes with IC50 of 117 nM. In an adoptive-transfer assay using OVA-sensitized splenocytes cultured in the presence of PD 171984, the latter inhibited BAL eosinophilic lung inflammation by 99.82% at a dose of 10 µM in mice. PD 171984 also inhibited active OVA-induced eosinophilic lung inflammation in mice dosed orally at 100 µM for 4

- days, suppressing BAL eosinophilia by 55.26%. Thus, I are potent MEK inhibitors that are useful in the prevention and treatment of asthma.
- ST diphenylamine std combinatorial prepn MEK inhibitor; bromophenylamino iodophenylamino benzamide prepn antiasthmatic
- IT Lung, disease  
(eosinophilia, treatment; preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT Combinatorial library  
Solid phase synthesis  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT Interleukin 5  
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors for the prevention and treatment of asthma)
- IT Antiasthmatics  
(treatment; preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors for the prevention and treatment of asthma)
- IT 212628-43-8P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-46-1P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-48-3P, 5-Chloro-2-(4-iodo-2-methylphenylamino)benzoic acid  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT 212628-44-9P, 3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-45-0P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-47-2P, 5-Chloro-2-(2-chloro-4-iodophenylamino)benzoic acid  
212628-49-4P, Sodium 5-Chloro-2-(4-iodo-2-methylphenylamino)benzoate  
212628-50-7P, 5-Bromo-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-51-8P, 2-(2-Chloro-4-iodophenylamino)-5-nitrobenzoic acid  
212628-52-9P 212628-53-0P, 2-(4-Iodo-2-methylphenylamino)-5-nitrobenzoic acid  
212628-54-1P, 2-(2-Fluoro-4-iodophenylamino)-5-nitrobenzoic acid  
212628-55-2P, 2-(4-Bromo-2-methylphenylamino)-4-fluorobenzoic acid  
212628-56-3P, 2-(2-Bromo-4-iodophenylamino)-5-nitrobenzoic acid  
212628-57-4P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluorobenzoic acid  
212628-58-5P, 3-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-59-6P, 3,4-Difluoro-2-(4-iodo-2-methoxyphenylamino)benzoic acid  
212628-60-9P, 4-Chloro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-61-0P, 2-(4-Iodo-2-methylphenylamino)benzoic acid 212628-62-1P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-63-2P, 5-Iodo-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-65-4P, 2,3,5-Trifluoro-4-(4-iodo-2-methylphenylamino)benzoic acid 212628-67-6P 212628-69-8P, 2-(4-Iodophenylamino)-5-methoxybenzoic acid 212628-71-2P, 3-Chloro-2-(2-chloro-4-iodophenylamino)benzoic acid 212628-72-3P, 2-Fluoro-6-(4-iodo-2-methylphenylamino)benzoic acid 212628-73-4P 212628-74-5P, 5-Methyl-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-75-6P, 2-Chloro-6-(4-iodo-2-methylphenylamino)benzoic acid 212628-76-7P, 2-(4-Iodo-2-methylphenylamino)-4-nitrobenzoic acid 212628-77-8P, 5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212628-78-9P 212628-79-0P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212628-80-3P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-methylbenzamide 212628-81-4P, N-Ethyl-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212628-82-5P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N,N-dimethylbenzamide 212628-83-6P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(1H-tetrazol-5-yl)-

benzamide 212628-84-7P, 5-Bromo-2-(4-iodo-2-methylphenylamino)benzamide  
212628-85-8P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N,N-  
dimethylbenzamide 212628-86-9P, [[5-Chloro-2-(4-iodo-2-  
methylphenylamino)benzoyl]amino]acetic acid 212628-87-0P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-propylbenzamide 212628-88-1P,  
5-Bromo-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide  
212628-89-2P, N,N-Diethyl-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide  
212628-90-5P, 4-Fluoro-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]propyl]-2-(4-  
iodo-2-methylphenylamino)benzamide 212628-91-6P, N,N-Diethyl-2-(4-iodo-2-  
methylphenylamino)-5-nitrobenzamide 212628-92-7P, N-Butyl-4-fluoro-2-(4-  
iodo-2-methylphenylamino)benzamide 212628-93-8P, 5-Chloro-N,N-diethyl-2-  
(4-iodo-2-methylphenylamino)benzamide 212628-94-9P, 5-Bromo-2-(4-iodo-2-  
methylphenylamino)-N,N-dimethylbenzamide 212628-95-0P 212628-96-1P,  
[5-Chloro-2-(4-iodo-2-methylphenylamino)phenyl]methanol 212628-97-2P,  
[2-(4-Iodo-2-methylphenylamino)-5-nitrophenyl]methanol 212628-98-3P,  
[5-Bromo-2-(4-iodo-2-methylphenylamino)phenyl]methanol 212628-99-4P,  
5-Bromo-3,4-difluoro-N-(2-hydroxyethyl)-2-(4-iodo-2-  
methylphenylamino)benzamide 212629-00-0P, N-(2,3-Dihydroxypropyl)-3,4-  
difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-01-1P,  
5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-  
ylethyl)benzamide 212629-02-2P, 3,4-Difluoro-N-(2-hydroxyethyl)-2-(4-  
iodo-2-methylphenylamino)benzamide 212629-03-3P, N-(2,3-Dihydroxypropyl)-  
4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-04-4P,  
3,4-Difluoro-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide  
212629-05-5P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-  
pyrrolidin-1-ylethyl)benzamide 212629-06-6P, 5-Bromo-3,4-difluoro-2-(4-  
iodo-2-methylphenylamino)-N-(2-pyridin-4-ylethyl)benzamide 212629-07-7P,  
4-Fluoro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide  
212629-08-8P, 5-Bromo-N-(3-dimethylaminopropyl)-3,4-difluoro-2-(4-iodo-2-  
methylphenylamino)benzamide 212629-09-9P, 5-Bromo-3,4-difluoro-2-(4-iodo-  
2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-10-2P,  
3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-  
ylethyl)benzamide 212629-11-3P, 3,4-Difluoro-2-(4-iodo-2-  
methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-12-4P,  
3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyridin-4-  
ylethyl)benzamide 212629-13-5P, N-(3-Dimethylaminopropyl)-3,4-difluoro-2-  
(4-iodo-2-methylphenylamino)benzamide 212629-14-6P, N-Benzyl-4-fluoro-2-  
(4-iodo-2-methylphenylamino)benzamide 212629-15-7P, 2-(4-Bromo-2-  
methylphenylamino)-3,4-difluoro-N-(2-hydroxyethyl)benzamide  
212629-16-8P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-  
ylethyl)benzamide 212629-17-9P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-  
N-(3-piperidin-1-ylpropyl)benzamide 212629-18-0P, 3,4-Difluoro-2-(4-iodo-  
2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-19-1P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-thiophen-2-ylethyl)benzamide  
212629-20-4P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-  
ylethyl)benzamide 212629-21-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-  
difluoro-N-(2-morpholin-4-ylethyl)benzamide 212629-22-6P,  
5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-pyridin-4-  
ylmethylbenzamide 212629-23-7P, 3,4-Difluoro-2-(4-iodo-2-  
methylphenylamino)-N-pyridin-4-ylmethylbenzamide 212629-24-8P,  
2-(4-Bromo-2-methylphenylamino)-N-(3-dimethylaminopropyl)-3,4-  
difluorobenzamide 212629-25-9P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-  
N-pyridin-4-ylmethylbenzamide 212629-26-0P, 4-Fluoro-2-(4-iodo-2-  
methylphenylamino)-N-(2-pyridin-4-ylethyl)benzamide 212629-27-1P,  
2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-pyridin-4-  
ylethyl)benzamide 212629-28-2P, 2-(4-Bromo-2-methylphenylamino)-3,4-  
difluoro-N-(3-hydroxypropyl)benzamide 212629-29-3P, 2-(4-Bromo-2-  
methylphenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-ylethyl)benzamide  
212629-30-6P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-phenethylbenzamide  
212629-31-7P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-thiophen-2-  
ylethyl)benzamide 212629-32-8P, 2-(4-Bromo-2-methylphenylamino)-3,4-  
difluoro-N-pyridin-4-ylmethylbenzamide 212629-33-9P,  
2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-phenethylbenzamide

212629-34-0P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-piperidin-1-ylethyl)benzamide 212629-35-1P, 5-Chloro-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]-propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-36-2P, 5-Fluoro-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]-propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-37-3P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-pyridin-4-ylmethylbenzamide 212629-38-4P, 5-Bromo-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]-propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-39-5P, 5-Chloro-N-(2-diethylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-40-8P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-41-9P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-42-0P, 5-Bromo-N-(2-diethylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-43-1P, N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-5-chloro-2-(4-iodo-2-methylphenylamino)benzamide 212629-44-2P, N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-5-bromo-2-(4-iodo-2-methylphenylamino)benzamide 212629-45-3P, 2-(4-Iodo-2-methylphenylamino)-5-nitrobenzoic acid phenethyl ester 212629-46-4P, N-[3-[4-(2-Hydroxyethyl)piperazin-1-yl]-propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-47-5P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-pyridin-4-ylmethylbenzamide 212629-48-6P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-50-0P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-52-2P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-54-4P, 5-Chloro-N-(3-dimethylaminopropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-56-6P, N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-58-8P, 5-Chloro-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-60-2P, 5-Chloro-N-[3-(N,N-diethylamino)-2-hydroxypropyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-62-4P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-64-6P, 5-Bromo-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-66-8P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-68-0P, N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212629-69-1P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-71-5P, 5-Chloro-N-(3-diethylaminopropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-73-7P, 5-Chloro-N-(2-diisopropylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-75-9P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-77-1P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-(2-piperidin-1-ylethyl)benzamide 212629-78-2P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-piperazin-1-ylethyl)benzamide 212629-79-3P, N-(2-Diethylaminoethyl)-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-80-6P, 5-Bromo-N-(3-dimethylaminopropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-81-7P, N-(3-Hydroxypropyl)-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212629-82-8P, 5-Fluoro-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-83-9P, N-(3-Diethylaminopropyl)-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-84-0P, N-(3-Diethylaminopropyl)-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212629-85-1P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-86-2P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-(3-piperidin-1-ylpropyl)benzamide 212629-87-3P, 5-Bromo-N-(2-diisopropylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-88-4P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-89-5P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-90-8P, N-[3-(N,N-Diethylamino)-2-hydroxypropyl]-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-91-9P 212629-92-0P 212629-93-1P, N-(2-Diisopropylaminoethyl)-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-94-2P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)thiobenzoic acid S-phenethyl ester 212629-95-3P,

5-Chloro-2-(4-iodo-2-methylphenylamino)thiobenzoic acid S-phenethyl ester  
212629-98-6P 212629-99-7P 212630-00-7P, N-Cyclopropyl-5-fluoro-2-(4-  
iodo-2-methylphenylamino)benzamide 212630-03-0P, 5-Fluoro-N-(2-  
hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212630-04-1P,  
N-Benzyloxy-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide  
212630-05-2P, N-Benzyloxy-5-bromo-2-(4-iodo-2-methylphenylamino)benzamide  
212630-06-3P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-(4-  
sulfamoylbenzyl)benzamide 212630-07-4P, N-(2-Hydroxyethyl)-5-iodo-2-(4-  
iodo-2-methylphenylamino)benzamide 212630-08-5P, N-(2-Hydroxyethyl)-2-(4-  
iodo-2-methylphenylamino)-5-nitrobenzamide 212630-09-6P,  
2-(4-Iodo-2-methylphenylamino)-N-methyl-5-nitro-N-phenylbenzamide  
212630-10-9P, 5-Chloro-N-cyclopropyl-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-11-0P, 5-Fluoro-2-(4-iodo-2-  
methylphenylamino)-N-methyl-N-phenylbenzamide 212630-12-1P,  
N-Allyl-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-13-2P,  
N-Benzyloxy-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-14-3P,  
5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(4-sulfamoylbenzyl)benzamide  
212630-15-4P, N-Allyl-5-chloro-2-(4-iodo-2-methylphenylamino)benzamide  
212630-16-5P, N-Cyclopropyl-2-(4-iodo-2-methylphenylamino)-5-  
nitrobenzamide 212630-17-6P, 5-Bromo-N-cyclopropyl-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-18-7P, 5-Chloro-2-(4-iodo-2-  
methylphenylamino)-N-methyl-N-phenylbenzamide 212630-19-8P,  
5-Iodo-2-(4-iodo-2-methylphenylamino)-N-(4-sulfamoylbenzyl)benzamide  
212630-20-1P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(4-  
sulfamoylbenzyl)benzamide 212630-21-2P, N-Allyl-2-(4-iodo-2-  
methylphenylamino)-5-nitrobenzamide 212630-22-3P, N-Allyl-5-bromo-2-(4-  
iodo-2-methylphenylamino)benzamide 212630-23-4P, 5-Fluoro-2-(4-iodo-2-  
methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-24-5P,  
N-Cyclopropyl-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide  
212630-25-6P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-methyl-N-  
phenylbenzamide 212630-26-7P, N-Benzyloxy-2-(4-iodo-2-methylphenylamino)-  
5-nitrobenzamide 212630-27-8P, N-Cyclohexyl-5-iodo-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-28-9P, N-Allyl-5-iodo-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-29-0P, 5-Iodo-2-(4-iodo-2-  
methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-30-3P,  
2-(4-Iodo-2-methylphenylamino)-N-(3-methylbenzyl)-5-nitrobenzamide  
212630-31-4P, 5-Iodo-2-(4-iodo-2-methylphenylamino)-N-methyl-N-  
phenylbenzamide 212630-32-5P, N-Cyclohexyl-5-fluoro-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-33-6P, 5-Chloro-N-cyclohexyl-2-(4-  
iodo-2-methylphenylamino)benzamide 212630-34-7P, 5-Bromo-2-(4-iodo-2-  
methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-35-8P,  
5-Bromo-N-cyclohexyl-2-(4-iodo-2-methylphenylamino)benzamide  
212630-36-9P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(3-  
methylbenzyl)benzamide 212630-37-0P, N-Cyclohexyl-2-(4-iodo-2-  
methylphenylamino)-5-nitrobenzamide 212630-38-1P 212630-39-2P,  
(4-Iodo-2-methylphenyl)-[2-(1H-tetrazol-5-yl)phenyl]amine 212630-41-6P,  
PD 170611 212630-42-7P, PD 171984 212630-43-8P, 2-(4-Bromo-2-  
methylphenylamino)-4-fluoro-N-hydroxybenzamide 212630-44-9P,  
5-Chloro-N-hydroxy-2-(4-iodo-2-methylphenylamino)-N-methylbenzamide  
212630-45-0P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(terahydropyran-2-  
yloxy)benzamide 212630-46-1P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-  
methoxybenzamide 212630-47-2P, 4-Fluoro-N-hydroxy-2-(4-fluoro-2-  
methylphenylamino)benzamide 212630-48-3P, 4-Fluoro-N-hydroxy-2-(2-  
methylphenylamino)benzamide 212630-49-4P, 4-Fluoro-2-(4-fluoro-2-  
methylphenylamino)-N-(terahydropyran-2-yloxy)benzamide 212630-50-7P,  
4-Fluoro-N-hydroxy-2-(4-chloro-2-methylphenylamino)benzamide  
212630-51-8P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-  
phenylmethoxybenzamide 212630-52-9P, 4-Fluoro-2-(4-iodo-2-  
methylphenylamino)-N-methoxybenzamide 212630-53-0P, 3,4-Difluoro-2-(4-  
iodo-2-methylphenylamino)-N-methoxybenzamide 212630-54-1P,  
2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-methoxybenzamide  
212630-55-2P, 2-(4-Bromo-2-methylphenylamino)-N-ethoxy-3,4-  
difluorobenzamide 212630-56-3P, 5-Bromo-N-ethoxy-3,4-difluoro-2-(4-iodo-

2-methylphenylamino)benzamide 212630-57-4P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-isopropoxybenzamide 212630-58-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-isopropoxybenzamide 212630-59-6P, 4-Fluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 212630-60-9P, 3,4-Difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 212630-61-0P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(furan-3-ylmethoxy)benzamide 212630-62-1P, 5-Bromo-3,4-difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 212630-63-2P, 5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-64-3P 212630-65-4P 212630-66-5P 212630-67-6P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(1-methyl-2-propyn-1-yloxy)benzamide 212630-68-7P 212630-69-8P 212630-70-1P 212630-71-2P 212630-72-3P 212630-73-4P 212630-74-5P 212630-75-6P 212630-76-7P 212630-77-8P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(3-methyl-5-phenylpent-2-en-4-ynyloxy)benzamide 212630-78-9P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(3-methyl-5-phenylpent-2-en-4-ynyloxy)benzamide 212630-79-0P, N-Ethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-80-3P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-propoxybenzamide 212630-81-4P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-propoxybenzamide 212630-82-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-propoxybenzamide 212630-83-6P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-propoxybenzamide 212630-84-7P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-isopropoxybenzamide 212630-85-8P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-isopropoxybenzamide 212630-86-9P, N-Cyclobutyloxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-87-0P, 2-(4-Bromo-2-methylphenylamino)-N-cyclobutyloxy-3,4-difluorobenzamide 212630-88-1P, N-Cyclopentyloxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-89-2P, 2-(4-Bromo-2-methylphenylamino)-N-cyclopentyloxy-3,4-difluorobenzamide 212630-90-5P, N-Cyclopropylmethoxy-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-91-6P, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-92-7P, 2-(4-Bromo-2-methylphenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide 212630-94-9P, PD 177168 212630-96-1P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-phenoxyethoxy)benzamide 212630-98-3P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-phenoxyethoxy)benzamide 212630-99-4P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-phenoxyethoxy)benzamide 212631-00-0P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(thiophen-2-ylmethoxy)benzamide 212631-01-1P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(thiophen-2-ylmethoxy)benzamide 212631-02-2P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(thiophen-2-ylmethoxy)benzamide 212631-03-3P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-methylallyloxy)benzamide 212631-04-4P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-methylallyloxy)benzamide 212631-05-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-methylallyloxy)benzamide

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)

IT 212631-06-6P, N-(But-2-enyloxy)-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212631-07-7P, N-(But-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212631-08-8P, 2-(4-Bromo-2-methylphenylamino)-N-(but-2-enyloxy)-3,4-difluorobenzamide 212631-09-9P 212631-13-5P 212631-15-7P, N-Cyclopentyloxy-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212631-28-2P 212631-29-3P 212631-33-9P 212631-35-1P 212631-36-2P, 5-Chloro-N-hydroxy-2-(4-iodo-2-methylphenylamino)benzamide 212631-37-3P 212631-38-4P 212631-39-5P 212631-40-8P 212631-41-9P 212631-42-0P 212631-43-1P 212631-44-2P

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 212631-49-7P 212631-50-0P 212631-51-1P 212631-52-2P 212631-53-3P  
 212631-54-4P 212631-55-5P 212631-56-6P 212631-57-7P, PD 185848  
 212631-58-8P 212631-59-9P 212631-60-2P 212631-61-3P, PD 198306  
 212631-62-4P, PD 298127 212631-63-5P 212631-64-6P 212631-65-7P  
 212631-66-8P 212631-67-9P, PD 184161 212631-68-0P 212631-69-1P  
 212631-70-4P, PD 297189 212631-71-5P 212631-72-6P 212631-73-7P  
 212631-74-8P 212631-75-9P 212631-76-0P 212631-77-1P 212631-78-2P,  
 PD 203311 212631-79-3P, PD 184352 212631-80-6P 212631-81-7P  
 219777-46-5P, N-(3-tert-Butylpropyn-2-yl)oxy-4-fluoro-2-(4-iodo-2-  
 methylphenylamino)benzamide 219777-60-3P, PD 188563 219778-04-8P, PD  
 185625 219778-52-6P, PD 180841 219794-13-5P 219794-21-5P,  
 2-(4-Iodo-2-methylphenylamino)-5-nitrothiobenzoic acid S-benzyl ester  
 277315-06-7P, (3-Hydroxypyrrolidin-1-yl)-[2-(4-iodo-2-methylphenylamino)-5-  
 nitrophenyl]methanone 277315-07-8P, [5-Bromo-2-(4-iodo-2-  
 methylphenylamino)phenyl]-(3-hydroxypyrrolidin-1-yl)-methanone  
 277315-08-9P, [5-Chloro-2-(4-iodo-2-methylphenylamino)phenyl]-(3-  
 hydroxypyrrolidin-1-yl)-methanone 277315-09-0P, [5-Fluoro-2-(4-iodo-2-  
 methylphenylamino)phenyl]-(3-hydroxypyrrolidin-1-yl)-methanone  
 277315-10-3P 277315-12-5P 277335-43-0P 278609-85-1P, PD 297190  
 278609-99-7P, PD 296711 278610-42-7P, PD 296770 278610-51-8P, PD  
 296767

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)

IT 352-33-0, 1-Chloro-4-fluorobenzene 1583-58-0, 2,4-Difluorobenzoic acid  
 6723-30-4, O-(Tetrahydro-2H-pyran-2-yl)-hydroxylamine 176317-02-5,  
 1-Bromo-2,3,4-trifluorobenzene

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)

IT 13194-68-8P, 2-Amino-5-iodotoluene 57381-34-7P, 5-Chloro-2-  
 fluorobenzonitrile 96515-79-6P, 5-Chloro-2-fluorobenzaldehyde  
 212631-82-8P, 5-Chloro-2-fluorobenzaldehyde oxime 212631-83-9P,  
 5-(5-Chloro-2-fluorophenyl)-1H-tetrazole 212631-84-0P 212631-85-1P,  
 5-Bromo-2,3,4-trifluorobenzoic acid 212631-86-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)

IT 142805-58-1

RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors for the prevention and treatment of asthma)

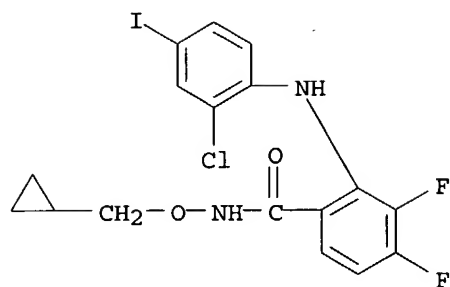
IT 212631-79-3P, PD 184352

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 17 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2000:441667 HCAPLUS

DN 133:58616

ED Entered STN: 30 Jun 2000

TI Preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivatives as MEK inhibitors

IN Gowan, Richard Carleton; Sebolt-Leopold, Judith

PA Warner-Lambert Company, USA

SO PCT Int. Appl., 115 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61P035-00

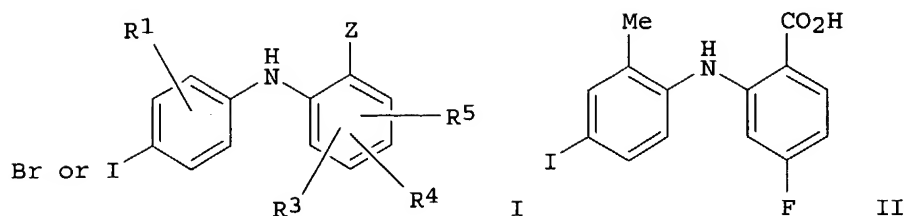
ICS A61K031-335; A61K031-35; A61K031-475; A61K031-335; A61K031-135;  
A61K031-475; A61K031-135; A61K031-335; A61K031-245; A61K031-475;  
A61K031-245; A61K031-335; A61K031-165; A61K031-475; A61K031-165;  
A61K031-35; A61K031-335; A61K031-475; A61K031-35

CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)

Section cross-reference(s): 1

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000037141	A1	20000629	WO 1999-US30485	19991221 <--
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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EP 1140291	A1	20011010	EP 1999-966523	19991221 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200101871	T2	20011022	TR 2001-200101871	19991221 <--
JP 2002532570	T2	20021002	JP 2000-589248	19991221 <--
EE 200100339	A	20021015	EE 2001-339	19991221 <--
ZA 2001004277	A	20020826	ZA 2001-4277	20010524 <--
NO 2001003099	A	20010820	NO 2001-3099	20010621 <--
HR 2001000473	A1	20020831	HR 2001-473	20010621 <--
BG 105715	A	20020430	BG 2001-105715	20010718 <--
PRAI US 1998-113291P	P	19981222 <--		
US 1999-164788P	P	19991110 <--		
WO 1999-US30485	W	19991221 <--		
OS MARPAT 133:58616				
GI				



AB The title compds. (I) [wherein R1 = H, OH, alkyl, alkoxy, halo, CF3, or CN; R3-R5 = independently H, OH, halo, CF3, alkyl, alkoxy, NO2, CN, or (O or NH)m-(CH2)n-R9, where R9 = H, OH, CO2H, or NR10R11; m = 0 or 1; n = 0-4; R10 and R11 = H, alkyl, or taken together with the N to which they are attached form a 3-10 membered ring; Z = CO2R7, tetrazolyl, CONR6R7, CONHNR10R11, or CH2OR7; R6 and R7 = independently H, (cyclo)alkyl, alkenyl, alkynyl, acyl, (hetero)aryl, or taken together with the N to which they are attached form a 3-10 membered ring, etc.] were prepared by standard or combinatorial synthetic methods involving the addition of halobenzoic

acids to haloanilines and optional reduction or amidation of the acid. Thus, treatment of 2-amino-5-iodotoluene in THF with LDA in THF/heptane/ethenylbenzene solution, followed by addition of

2,4-difluorobenzoic acid in THF afforded II. Combination chemotherapy of I with a known mitotic agent caused dramatic increases of apoptosis of colon and lung carcinoma cells. For instance, 2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide (PD 184352) in combination with paclitaxel resulted in 44% to 55% apoptosis, 6% to 18% increases over using either agent alone, of colon 26 carcinoma, HT-29 colon carcinoma, and A549 lung carcinoma cells.

ST diphenylamine std combinatorial prepn MEK inhibitor; bromophenylamino iodophenylamino benzamide prepn anticancer agent; benzamide bromophenylamino iodophenylamino prepn mitotic agent combination chemotherapy

IT Apoptosis  
(increased efficacy in treatment of cancer with combination chemotherapeutics comprised of compns. of MEK inhibitors and known mitotic inhibitors)

IT Combinatorial library  
Solid phase synthesis  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)

IT Antitumor agents  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors for use in combination with known mitotic inhibitors as anticancer agents)

IT 33069-62-4, Paclitaxel  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(increased efficacy in treatment of cancer with combination chemotherapeutics comprised of compns. of MEK inhibitors and known mitotic inhibitors)

IT 57-22-7, Vincristine 865-21-4, Vinblastine 71486-22-1, Vinorelbine 114977-28-5, Docetaxel 162652-95-1, Vinflunine

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(increased efficacy in treatment of cancer with combination chemotherapeutics comprised of compns. of MEK inhibitors and known mitotic inhibitors)

- IT 212628-43-8P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-46-1P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-48-3P, 5-Chloro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212630-41-6P, 4-Fluoro-N-hydroxy-2-(4-iodo-2-methylphenylamino)benzamide  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT 212628-44-9P, 3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-45-0P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-47-2P, 5-Chloro-2-(2-chloro-4-iodophenylamino)benzoic acid  
212628-49-4P, Sodium 5-Chloro-2-(4-iodo-2-methylphenylamino)benzoate  
212628-50-7P, 5-Bromo-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-51-8P, 2-(2-Chloro-4-iodophenylamino)-5-nitrobenzoic acid  
212628-52-9P, 212628-53-0P, 2-(4-Iodo-2-methylphenylamino)-5-nitrobenzoic acid  
212628-54-1P, 2-(2-Fluoro-4-iodophenylamino)-5-nitrobenzoic acid  
212628-55-2P, 2-(4-Bromo-2-methylphenylamino)-4-fluorobenzoic acid  
212628-56-3P, 2-(2-Bromo-4-iodophenylamino)-5-nitrobenzoic acid  
212628-57-4P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluorobenzoic acid  
212628-58-5P, 3-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-59-6P, 3,4-Difluoro-2-(4-iodo-2-methoxyphenylamino)benzoic acid  
212628-60-9P, 4-Chloro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-61-0P, 2-(4-Iodo-2-methylphenylamino)benzoic acid 212628-62-1P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-63-2P, 5-Iodo-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-65-4P, 2,3,5-Trifluoro-4-(4-iodo-2-methylphenylamino)benzoic acid 212628-67-6P, 212628-69-8P, 2-(4-Iodophenylamino)-5-methoxybenzoic acid 212628-71-2P, 3-Chloro-2-(2-chloro-4-iodophenylamino)benzoic acid 212628-72-3P, 2-Fluoro-6-(4-iodo-2-methylphenylamino)benzoic acid 212628-73-4P, 212628-74-5P, 5-Methyl-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-75-6P, 2-Chloro-6-(4-iodo-2-methylphenylamino)benzoic acid 212628-76-7P, 2-(4-Iodo-2-methylphenylamino)-4-nitrobenzoic acid 212628-77-8P, 5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212628-78-9P, 212628-79-0P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212628-80-3P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-methylbenzamide 212628-81-4P, N-Ethyl-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212628-82-5P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N,N-dimethylbenzamide 212628-83-6P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(1H-tetrazol-5-yl)-benzamide 212628-84-7P, 5-Bromo-2-(4-iodo-2-methylphenylamino)benzamide 212628-85-8P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N,N-dimethylbenzamide 212628-86-9P, [[5-Chloro-2-(4-iodo-2-methylphenylamino)benzoyl]amino]acetic acid 212628-87-0P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-propylbenzamide 212628-88-1P, 5-Bromo-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212628-89-2P, N,N-Diethyl-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212628-90-5P, 4-Fluoro-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212628-91-6P, N,N-Diethyl-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212628-92-7P, N-Butyl-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212628-93-8P, 5-Chloro-N,N-diethyl-2-(4-iodo-2-methylphenylamino)benzamide 212628-94-9P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N,N-dimethylbenzamide 212628-95-0P, 212628-96-1P, [5-Chloro-2-(4-iodo-2-methylphenylamino)phenyl]methanol 212628-97-2P, [2-(4-Iodo-2-methylphenylamino)-5-nitrophenyl]methanol 212628-98-3P, [5-Bromo-2-(4-iodo-2-methylphenylamino)phenyl]methanol 212628-99-4P, 5-Bromo-3,4-difluoro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-00-0P, N-(2,3-Dihydroxypropyl)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-01-1P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-02-2P, 3,4-Difluoro-N-(2-hydroxyethyl)-2-(4-

iodo-2-methylphenylamino)benzamide 212629-03-3P, N-(2,3-Dihydroxypropyl)-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-04-4P, 3,4-Difluoro-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-05-5P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-06-6P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyridin-4-ylethyl)benzamide 212629-07-7P, 4-Fluoro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-08-8P, 5-Bromo-N-(3-dimethylaminopropyl)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-09-9P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-10-2P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-11-3P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-12-4P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyridin-4-ylethyl)benzamide 212629-13-5P, N-(3-Dimethylaminopropyl)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-14-6P, N-Benzyl-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-15-7P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-hydroxyethyl)benzamide 212629-16-8P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-17-9P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-18-0P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-19-1P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-thiophen-2-ylethyl)benzamide 212629-20-4P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-21-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-morpholin-4-ylethyl)benzamide 212629-22-6P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-pyridin-4-ylmethylbenzamide 212629-23-7P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-pyridin-4-ylmethylbenzamide 212629-24-8P, 2-(4-Bromo-2-methylphenylamino)-N-(3-dimethylaminopropyl)-3,4-difluorobenzamide 212629-25-9P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-pyridin-4-ylmethylbenzamide 212629-26-0P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyridin-4-ylethyl)benzamide 212629-27-1P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-pyridin-4-ylethyl)benzamide 212629-28-2P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(3-hydroxypropyl)benzamide 212629-29-3P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-30-6P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-phenethylbenzamide 212629-31-7P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-thiophen-2-ylethyl)benzamide 212629-32-8P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-pyridin-4-ylmethylbenzamide 212629-33-9P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-phenethylbenzamide 212629-34-0P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-piperidin-1-ylethyl)benzamide 212629-35-1P, 5-Chloro-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]-propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-36-2P, 5-Fluoro-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]-propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-37-3P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-pyridin-4-ylmethylbenzamide 212629-38-4P, 5-Bromo-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]-propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-39-5P, 5-Chloro-N-(2-diethylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-40-8P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-41-9P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-42-0P, 5-Bromo-N-(2-diethylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-43-1P, N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-5-chloro-2-(4-iodo-2-methylphenylamino)benzamide 212629-44-2P, N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-5-bromo-2-(4-iodo-2-methylphenylamino)benzamide 212629-45-3P, 2-(4-Iodo-2-methylphenylamino)-5-nitrobenzoic acid phenethyl ester 212629-46-4P, N-[3-[4-(2-Hydroxyethyl)piperazin-1-yl]-propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-47-5P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-pyridin-4-ylmethylbenzamide 212629-48-6P,

5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide  
212629-50-0P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-52-2P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-54-4P, 5-Chloro-N-(3-dimethylaminopropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-56-6P, N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-58-8P, 5-Chloro-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-60-2P, 5-Chloro-N-[3-(N,N-diethylamino)-2-hydroxypropyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-62-4P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-64-6P, 5-Bromo-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-66-8P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-68-0P, N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212629-69-1P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-71-5P, 5-Chloro-N-(3-diethylaminopropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-73-7P, 5-Chloro-N-(2-diisopropylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-75-9P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-77-1P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-(2-piperidin-1-ylethyl)benzamide 212629-78-2P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-piperazin-1-ylethyl)benzamide 212629-79-3P, N-(2-Diethylaminoethyl)-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-80-6P, 5-Bromo-N-(3-dimethylaminopropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-81-7P, N-(3-Hydroxypropyl)-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212629-82-8P, 5-Fluoro-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-83-9P, N-(3-Diethylaminopropyl)-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-84-0P, N-(3-Diethylaminopropyl)-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212629-85-1P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-86-2P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-(3-piperidin-1-ylpropyl)benzamide 212629-87-3P, 5-Bromo-N-(2-diisopropylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-88-4P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-89-5P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-90-8P, N-[3-(N,N-Diethylamino)-2-hydroxypropyl]-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-91-9P 212629-92-0P 212629-93-1P, N-(2-Diisopropylaminoethyl)-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-94-2P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)thiobenzoic acid S-phenethyl ester 212629-95-3P, 5-Chloro-2-(4-iodo-2-methylphenylamino)thiobenzoic acid S-phenethyl ester 212629-98-6P 212629-99-7P 212630-00-7P, N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-03-0P, 5-Fluoro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212630-04-1P, N-Benzoyloxy-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-05-2P, N-Benzoyloxy-5-bromo-2-(4-iodo-2-methylphenylamino)benzamide 212630-06-3P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-(4-sulfamoylbenzyl)benzamide 212630-07-4P, N-(2-Hydroxyethyl)-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-08-5P, N-(2-Hydroxyethyl)-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-09-6P, 2-(4-Iodo-2-methylphenylamino)-N-methyl-5-nitro-N-phenylbenzamide 212630-10-9P, 5-Chloro-N-cyclopropyl-2-(4-iodo-2-methylphenylamino)benzamide 212630-11-0P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-methyl-N-phenylbenzamide 212630-12-1P, N-Allyl-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-13-2P, N-Benzoyloxy-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-14-3P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(4-sulfamoylbenzyl)benzamide 212630-15-4P, N-Allyl-5-chloro-2-(4-iodo-2-methylphenylamino)benzamide 212630-16-5P, N-Cyclopropyl-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-17-6P, 5-Bromo-N-cyclopropyl-2-(4-iodo-2-methylphenylamino)benzamide 212630-18-7P, 5-Chloro-2-(4-iodo-2-

methylphenylamino)-N-methyl-N-phenylbenzamide 212630-19-8P,  
5-Iodo-2-(4-iodo-2-methylphenylamino)-N-(4-sulfamoylbenzyl)benzamide  
212630-20-1P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(4-  
sulfamoylbenzyl)benzamide 212630-21-2P, N-Allyl-2-(4-iodo-2-  
methylphenylamino)-5-nitrobenzamide 212630-22-3P, N-Allyl-5-bromo-2-(4-  
iodo-2-methylphenylamino)benzamide 212630-23-4P, 5-Fluoro-2-(4-iodo-2-  
methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-24-5P,  
N-Cyclopropyl-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide  
212630-25-6P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-methyl-N-  
phenylbenzamide 212630-26-7P, N-Benzyloxy-2-(4-iodo-2-methylphenylamino)-  
5-nitrobenzamide 212630-27-8P, N-Cyclohexyl-5-iodo-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-28-9P, N-Allyl-5-iodo-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-29-0P, 5-Iodo-2-(4-iodo-2-  
methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-30-3P,  
2-(4-Iodo-2-methylphenylamino)-N-(3-methylbenzyl)-5-nitrobenzamide  
212630-31-4P, 5-Iodo-2-(4-iodo-2-methylphenylamino)-N-methyl-N-  
phenylbenzamide 212630-32-5P, N-Cyclohexyl-5-fluoro-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-33-6P, 5-Chloro-N-cyclohexyl-2-(4-  
iodo-2-methylphenylamino)benzamide 212630-34-7P, 5-Bromo-2-(4-iodo-2-  
methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-35-8P,  
5-Bromo-N-cyclohexyl-2-(4-iodo-2-methylphenylamino)benzamide  
212630-36-9P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(3-  
methylbenzyl)benzamide 212630-37-0P, N-Cyclohexyl-2-(4-iodo-2-  
methylphenylamino)-5-nitrobenzamide 212630-38-1P 212630-39-2P,  
(4-Iodo-2-methylphenyl)-[2-(1H-tetrazol-5-yl)phenyl]amine 212630-42-7P,  
5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methylphenylamino)benzamide  
212630-43-8P, 2-(4-Bromo-2-methylphenylamino)-4-fluoro-N-hydroxybenzamide  
212630-44-9P, 5-Chloro-N-hydroxy-2-(4-iodo-2-methylphenylamino)-N-  
methylbenzamide 212630-45-0P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-  
(terahydropyran-2-yloxy)benzamide 212630-46-1P, 5-Chloro-2-(4-iodo-2-  
methylphenylamino)-N-methoxybenzamide 212630-47-2P, 4-Fluoro-N-hydroxy-2-  
(4-fluoro-2-methylphenylamino)benzamide 212630-48-3P,  
4-Fluoro-N-hydroxy-2-(2-methylphenylamino)benzamide 212630-49-4P,  
4-Fluoro-2-(4-fluoro-2-methylphenylamino)-N-(terahydropyran-2-  
yloxy)benzamide 212630-50-7P, 4-Fluoro-N-hydroxy-2-(4-chloro-2-  
methylphenylamino)benzamide 212630-51-8P, 4-Fluoro-2-(4-iodo-2-  
methylphenylamino)-N-phenylmethoxybenzamide 212630-52-9P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-methoxybenzamide 212630-53-0P,  
3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-methoxybenzamide  
212630-54-1P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-  
methoxybenzamide 212630-55-2P, 2-(4-Bromo-2-methylphenylamino)-N-ethoxy-  
3,4-difluorobenzamide 212630-56-3P, 5-Bromo-N-ethoxy-3,4-difluoro-2-(4-  
iodo-2-methylphenylamino)benzamide 212630-57-4P, 3,4-Difluoro-2-(4-iodo-  
2-methylphenylamino)-N-isopropoxybenzamide 212630-58-5P,  
2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-isopropoxybenzamide  
212630-59-6P, 4-Fluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-60-9P, 3,4-Difluoro-N-(furan-3-  
ylmethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 212630-61-0P,  
2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(furan-3-  
ylmethoxy)benzamide 212630-62-1P, 5-Bromo-3,4-difluoro-N-(furan-3-  
ylmethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 212630-63-2P,  
5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-64-3P 212630-65-4P 212630-66-5P  
212630-67-6P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(1-methyl-2-  
propyn-1-yloxy)benzamide 212630-68-7P 212630-69-8P 212630-70-1P  
212630-71-2P 212630-72-3P 212630-73-4P 212630-74-5P 212630-75-6P  
212630-76-7P 212630-77-8P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-  
(3-methyl-5-phenylpent-2-en-4-ynyloxy)benzamide 212630-78-9P,  
2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(3-methyl-5-phenylpent-2-en-  
4-ynyloxy)benzamide 212630-79-0P, N-Ethoxy-3,4-difluoro-2-(4-iodo-2-  
methylphenylamino)benzamide 212630-80-3P, 4-Fluoro-2-(4-iodo-2-  
methylphenylamino)-N-propoxybenzamide 212630-81-4P, 3,4-Difluoro-2-(4-  
iodo-2-methylphenylamino)-N-propoxybenzamide 212630-82-5P,

2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-propoxybenzamide  
 212630-83-6P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-propoxybenzamide 212630-84-7P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-isopropoxybenzamide 212630-85-8P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-isopropoxybenzamide 212630-86-9P, N-Cyclobutyloxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-87-0P, 2-(4-Bromo-2-methylphenylamino)-N-cyclobutyloxy-3,4-difluorobenzamide 212630-88-1P, N-Cyclopentyloxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-89-2P, 2-(4-Bromo-2-methylphenylamino)-N-cyclopentyloxy-3,4-difluorobenzamide 212630-90-5P, N-Cyclopropylmethoxy-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-91-6P, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-92-7P, 2-(4-Bromo-2-methylphenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide 212630-94-9P 212630-96-1P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-phenoxyethoxy)benzamide 212630-98-3P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-phenoxyethoxy)benzamide 212630-99-4P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-phenoxyethoxy)benzamide 212631-00-0P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(thiophen-2-ylmethoxy)benzamide 212631-01-1P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(thiophen-2-ylmethoxy)benzamide 212631-02-2P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(thiophen-2-ylmethoxy)benzamide 212631-03-3P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-methylallyloxy)benzamide 212631-04-4P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-methylallyloxy)benzamide 212631-05-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-methylallyloxy)benzamide 212631-06-6P, N-(But-2-enyloxy)-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide

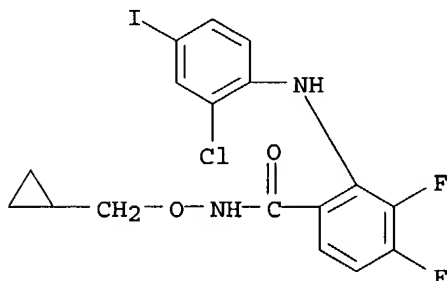
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)

IT 212631-07-7P, N-(But-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212631-08-8P, 2-(4-Bromo-2-methylphenylamino)-N-(but-2-enyloxy)-3,4-difluorobenzamide 212631-09-9P 212631-13-5P 212631-15-7P, N-Cyclopentyloxy-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212631-28-2P 212631-29-3P 212631-33-9P 212631-35-1P 212631-36-2P, 5-Chloro-N-hydroxy-2-(4-iodo-2-methylphenylamino)benzamide 212631-37-3P 212631-38-4P 212631-39-5P 212631-40-8P 212631-41-9P 212631-42-0P 212631-43-1P 212631-44-2P 212631-45-3P 212631-46-4P 212631-47-5P 212631-48-6P 212631-49-7P 212631-50-0P 212631-51-1P 212631-52-2P 212631-53-3P 212631-54-4P 212631-55-5P 212631-56-6P 212631-57-7P 212631-58-8P 212631-59-9P 212631-60-2P 212631-61-3P 212631-62-4P 212631-63-5P 212631-64-6P 212631-65-7P 212631-66-8P 212631-67-9P 212631-68-0P 212631-69-1P 212631-71-5P 212631-72-6P 212631-73-7P 212631-74-8P 212631-75-9P 212631-76-0P 212631-77-1P 212631-78-2P 212631-79-3P 212631-80-6P 212631-81-7P 219777-46-5P, N-(3-tert-Butylpropyn-2-yl)oxy-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 219777-60-3P 219778-04-8P 219778-52-6P 219794-13-5P 219794-21-5P, 2-(4-Iodo-2-methylphenylamino)-5-nitrothiobenzoic acid S-benzyl ester 277315-06-7P, (3-Hydroxypyrrolidin-1-yl)-[2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]methanone 277315-07-8P, [5-Bromo-2-(4-iodo-2-methylphenylamino)phenyl]-(3-hydroxypyrrolidin-1-yl)-methanone 277315-08-9P, [5-Chloro-2-(4-iodo-2-methylphenylamino)phenyl]-(3-hydroxypyrrolidin-1-yl)-methanone 277315-09-0P, [5-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-(3-hydroxypyrrolidin-1-yl)-methanone 277315-10-3P 277315-12-5P 277335-43-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

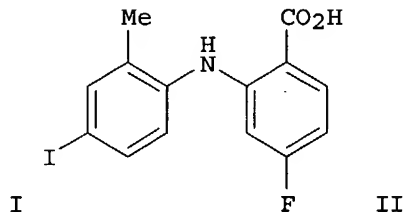
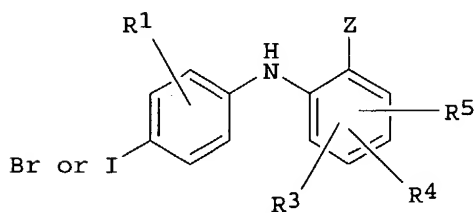
- (preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT 352-33-0, 1-Chloro-4-fluorobenzene 1583-58-0, 2,4-Difluorobenzoic acid  
6723-30-4, O-(Tetrahydro-2H-pyran-2-yl)-hydroxylamine 176317-02-5,  
1-Bromo-2,3,4-trifluorobenzene  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT 13194-68-8P, 2-Amino-5-iodotoluene 57381-34-7P, 5-Chloro-2-fluorobenzonitrile 96515-79-6P, 5-Chloro-2-fluorobenzaldehyde 212631-82-8P, 5-Chloro-2-fluorobenzaldehyde oxime 212631-83-9P, 5-(5-Chloro-2-fluorophenyl)-1H-tetrazole 212631-84-0P 212631-85-1P, 5-Bromo-2,3,4-trifluorobenzoic acid 212631-86-2P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT 142805-58-1  
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors for use in combination with known mitotic inhibitors as anticancer agents)
- RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
- RE
- (1) Ciba Geigy Ag; WO 9732604 A 1997 HCAPLUS
  - (2) Cowser, L; US 5959097 A 1999 HCAPLUS
  - (3) de Souza; BRITISH JOURNAL OF CANCER 1997, V75(11), P1593 HCAPLUS
  - (4) Johnson, B; US 6002008 A 1999 HCAPLUS
  - (5) Lieu; CELL GROWTH & DIFFERENTIATION 1998, V9(9), P767 HCAPLUS
  - (6) Univ Texas; WO 9842830 A 1998 HCAPLUS
  - (7) Wang; BIOCHEMICAL PHARMACOLOGY 1998, V56(5), P635 HCAPLUS
  - (8) Warner Lambert Co; WO 9519970 A 1995 HCAPLUS
  - (9) Warner Lambert Co; WO 9837881 A 1998 HCAPLUS
  - (10) Wen-Ching, H; US 6040321 A 2000 HCAPLUS
- IT 212631-79-3P  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- RN 212631-79-3 HCAPLUS
- CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 18 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN  
 AN 2000:420949 HCAPLUS  
 DN 133:73860  
 ED Entered STN: 23 Jun 2000  
 TI Preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivatives  
 as MEK inhibitors  
 IN Dudley, David Thomas; Flory, Craig Mason; Saltiel, Alan Robert  
 PA Warner-Lambert Company, USA  
 SO PCT Int. Appl., 106 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 IC ICM A61K031-00  
 CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)  
 Section cross-reference(s): 1, 63

## FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000035436	A2	20000622	WO 1999-US29783	19991215 <--
	WO 2000035436	A3	20011018		
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	EP 1143957	A2	20011017	EP 1999-966278	19991215 <--
	EP 1143957	A3	20020227		
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	US 1999-164651P	P	19991110	<--	
	WO 1999-US29783	W	19991215	<--	
OS	MARPAT 133:73860				
GI					



AB The title compds. (I) [wherein R1 = H, OH, alkyl, alkoxy, halo, CF3, or CN; R3-R5 = independently H, OH, halo, CF3, alkyl, alkoxy, NO2, CN, or (O or NH)m-(CH2)n-R9, where R9 = H, OH, CO2H, or NR10R11; m = 0 or 1; n = 0-4; R10 and R11 = H, alkyl, or taken together with the N to which they are attached form a 3-10 membered ring; Z = CO2R7, tetrazolyl, CONR6R7, CONHNR10R11, or CH2OR7; R6 and R7 = independently H, (cyclo)alkyl, alkenyl, alkynyl, acyl, (hetero)aryl, or taken together with the N to which they are attached form a 3-10 membered ring, etc.] were prepared by standard or combinatorial synthetic methods involving the addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid. For

- example, treatment of 2-amino-5-iodotoluene in THF with LDA in THF/heptane/ethenylbenzene solution, followed by addition of 2,4-difluorobenzoic acid in THF afforded II. In assays against type II collagen induced arthritis in mice and monoarticular arthritis in rats, I showed potent anti-arthritic activity. I inhibited IL-1 induced stromelysin production in rabbit synovial fibroblast cell cultures with IC50 from 9 nM to 192 nM. Interleukin 1-alpha stimulated cartilage degradation was reduced by up to 75% in New Zealand white rabbits upon administration of I. Thus, I are potent MEK inhibitors useful in the prevention and treatment of rheumatoid arthritis or osteoarthritis.
- ST diphenylamine std combinatorial prepn MEK inhibitor; bromophenylamino iodophenylamino benzamide prepn antiarthritic
- IT Antiarthritics  
Antirheumatic agents  
Combinatorial library  
Solid phase synthesis  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT Interleukin 1  
Interleukin 2  
Proteoglycans, biological studies  
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT 212628-43-8P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-46-1P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-48-3P, 5-Chloro-2-(4-iodo-2-methylphenylamino)benzoic acid  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT 212628-44-9P, 3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-45-0P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-47-2P, 5-Chloro-2-(2-chloro-4-iodophenylamino)benzoic acid  
212628-49-4P, Sodium 5-Chloro-2-(4-iodo-2-methylphenylamino)benzoate  
212628-50-7P, 5-Bromo-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-51-8P, 2-(2-Chloro-4-iodophenylamino)-5-nitrobenzoic acid  
212628-52-9P, 212628-53-0P, 2-(4-Iodo-2-methylphenylamino)-5-nitrobenzoic acid  
212628-54-1P, 2-(2-Fluoro-4-iodophenylamino)-5-nitrobenzoic acid  
212628-55-2P, 2-(4-Bromo-2-methylphenylamino)-4-fluorobenzoic acid  
212628-56-3P, 2-(2-Bromo-4-iodophenylamino)-5-nitrobenzoic acid  
212628-57-4P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluorobenzoic acid  
212628-58-5P, 3-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-59-6P, 3,4-Difluoro-2-(4-iodo-2-methoxyphenylamino)benzoic acid  
212628-60-9P, 4-Chloro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-61-0P, 2-(4-Iodo-2-methylphenylamino)benzoic acid 212628-62-1P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-63-2P, 5-Iodo-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-65-4P, 2,3,5-Trifluoro-4-(4-iodo-2-methylphenylamino)benzoic acid 212628-67-6P, 212628-69-8P, 2-(4-Iodophenylamino)-5-methoxybenzoic acid 212628-71-2P, 3-Chloro-2-(2-chloro-4-iodophenylamino)benzoic acid 212628-72-3P, 2-Fluoro-6-(4-iodo-2-methylphenylamino)benzoic acid 212628-73-4P, 212628-74-5P, 5-Methyl-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-75-6P, 2-Chloro-6-(4-iodo-2-methylphenylamino)benzoic acid  
212628-76-7P, 2-(4-Iodo-2-methylphenylamino)-4-nitrobenzoic acid  
212628-77-8P, 5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-

methylphenylamino)benzamide 212628-78-9P 212628-79-0P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212628-80-3P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-methylbenzamide 212628-81-4P,  
N-Ethyl-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212628-82-5P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)-N,N-dimethylbenzamide  
212628-83-6P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(1H-tetrazol-5-yl)-  
benzamide 212628-84-7P, 5-Bromo-2-(4-iodo-2-methylphenylamino)benzamide  
212628-85-8P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N,N-  
dimethylbenzamide 212628-86-9P, [[5-Chloro-2-(4-iodo-2-  
methylphenylamino)benzoyl]amino]acetic acid 212628-87-0P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-propylbenzamide 212628-88-1P,  
5-Bromo-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide  
212628-89-2P, N,N-Diethyl-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide  
212628-90-5P, 4-Fluoro-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]propyl]-2-(4-  
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[5-Chloro-2-(4-iodo-2-methylphenylamino)phenyl]methanol 212628-97-2P,  
[2-(4-Iodo-2-methylphenylamino)-5-nitrophenyl]methanol 212628-98-3P,  
[5-Bromo-2-(4-iodo-2-methylphenylamino)phenyl]methanol 212628-99-4P,  
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4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-04-4P,  
3,4-Difluoro-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide  
212629-05-5P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-  
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iodo-2-methylphenylamino)-N-(2-pyridin-4-ylethyl)benzamide 212629-07-7P,  
4-Fluoro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide  
212629-08-8P, 5-Bromo-N-(3-dimethylaminopropyl)-3,4-difluoro-2-(4-iodo-2-  
methylphenylamino)benzamide 212629-09-9P, 5-Bromo-3,4-difluoro-2-(4-iodo-  
2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-10-2P,  
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3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyridin-4-  
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methylphenylamino)-3,4-difluoro-N-(2-hydroxyethyl)benzamide  
212629-16-8P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-  
ylethyl)benzamide 212629-17-9P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-  
N-(3-piperidin-1-ylpropyl)benzamide 212629-18-0P, 3,4-Difluoro-2-(4-iodo-  
2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-19-1P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-thiophen-2-ylethyl)benzamide  
212629-20-4P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-  
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2-(4-Bromo-2-methylphenylamino)-N-(3-dimethylaminopropyl)-3,4-  
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N-pyridin-4-ylmethylbenzamide 212629-26-0P, 4-Fluoro-2-(4-iodo-2-  
methylphenylamino)-N-(2-pyridin-4-ylethyl)benzamide 212629-27-1P,  
2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-pyridin-4-  
ylethyl)benzamide 212629-28-2P, 2-(4-Bromo-2-methylphenylamino)-3,4-  
difluoro-N-(3-hydroxypropyl)benzamide 212629-29-3P, 2-(4-Bromo-2-

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212629-31-7P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-thiophen-2-ylethyl)benzamide 212629-32-8P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-pyridin-4-ylmethylbenzamide 212629-33-9P,  
2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-phenethylbenzamide  
212629-34-0P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-piperidin-1-ylethyl)benzamide 212629-35-1P, 5-Chloro-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]-propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-36-2P, 5-Fluoro-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]-propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-37-3P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-pyridin-4-ylmethylbenzamide 212629-38-4P,  
5-Bromo-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]-propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-39-5P, 5-Chloro-N-(2-diethylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-40-8P,  
5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-41-9P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-42-0P, 5-Bromo-N-(2-diethylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-43-1P, N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-5-chloro-2-(4-iodo-2-methylphenylamino)benzamide 212629-44-2P, N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-5-bromo-2-(4-iodo-2-methylphenylamino)benzamide 212629-45-3P, 2-(4-Iodo-2-methylphenylamino)-5-nitrobenzoic acid phenethyl ester 212629-46-4P, N-[3-[4-(2-Hydroxyethyl)piperazin-1-yl]-propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-47-5P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-pyridin-4-ylmethylbenzamide 212629-48-6P,  
5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-50-0P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-52-2P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-54-4P, 5-Chloro-N-(3-dimethylaminopropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-56-6P, N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-58-8P, 5-Chloro-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-60-2P, 5-Chloro-N-[3-(N,N-diethylamino)-2-hydroxypropyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-62-4P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-64-6P, 5-Bromo-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-66-8P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-68-0P,  
N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212629-69-1P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-71-5P, 5-Chloro-N-(3-diethylaminopropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-73-7P, 5-Chloro-N-(2-diisopropylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-75-9P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-77-1P,  
2-(4-Iodo-2-methylphenylamino)-5-nitro-N-(2-piperidin-1-ylethyl)benzamide 212629-78-2P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-piperazin-1-ylethyl)benzamide 212629-79-3P, N-(2-Diethylaminoethyl)-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-80-6P, 5-Bromo-N-(3-dimethylaminopropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-81-7P, N-(3-Hydroxypropyl)-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212629-82-8P, 5-Fluoro-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-83-9P, N-(3-Diethylaminopropyl)-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-84-0P,  
N-(3-Diethylaminopropyl)-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212629-85-1P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-86-2P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-(3-piperidin-1-ylpropyl)benzamide 212629-87-3P, 5-Bromo-N-(2-diisopropylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-88-4P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-89-5P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-

N-(3-piperidin-1-ylpropyl)benzamide 212629-90-8P, N-[3-(N,N-Diethylamino)-2-hydroxypropyl]-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-91-9P 212629-92-0P 212629-93-1P, N-(2-Diisopropylaminoethyl)-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-94-2P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)thiobenzoic acid S-phenethyl ester 212629-95-3P, 5-Chloro-2-(4-iodo-2-methylphenylamino)thiobenzoic acid S-phenethyl ester 212629-98-6P 212629-99-7P 212630-00-7P, N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-03-0P, 5-Fluoro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212630-04-1P, N-Benzyloxy-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-05-2P, N-Benzyloxy-5-bromo-2-(4-iodo-2-methylphenylamino)benzamide 212630-06-3P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-(4-sulfamoylbenzyl)benzamide 212630-07-4P, N-(2-Hydroxyethyl)-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-08-5P, N-(2-Hydroxyethyl)-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-09-6P, 2-(4-Iodo-2-methylphenylamino)-N-methyl-5-nitro-N-phenylbenzamide 212630-10-9P, 5-Chloro-N-cyclopropyl-2-(4-iodo-2-methylphenylamino)benzamide 212630-11-0P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-methyl-N-phenylbenzamide 212630-12-1P, N-Allyl-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-13-2P, N-Benzyloxy-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-14-3P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(4-sulfamoylbenzyl)benzamide 212630-15-4P, N-Allyl-5-chloro-2-(4-iodo-2-methylphenylamino)benzamide 212630-16-5P, N-Cyclopropyl-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-17-6P, 5-Bromo-N-cyclopropyl-2-(4-iodo-2-methylphenylamino)benzamide 212630-18-7P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-methyl-N-phenylbenzamide 212630-19-8P, 5-Iodo-2-(4-iodo-2-methylphenylamino)-N-(4-sulfamoylbenzyl)benzamide 212630-20-1P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(4-sulfamoylbenzyl)benzamide 212630-21-2P, N-Allyl-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-22-3P, N-Allyl-5-bromo-2-(4-iodo-2-methylphenylamino)benzamide 212630-23-4P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-24-5P, N-Cyclopropyl-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-25-6P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-methyl-N-phenylbenzamide 212630-26-7P, N-Benzyloxy-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-27-8P, N-Cyclohexyl-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-28-9P, N-Allyl-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-29-0P, 5-Iodo-2-(4-iodo-2-methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-30-3P, 2-(4-Iodo-2-methylphenylamino)-N-(3-methylbenzyl)-5-nitrobenzamide 212630-31-4P, 5-Iodo-2-(4-iodo-2-methylphenylamino)-N-methyl-N-phenylbenzamide 212630-32-5P, N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-33-6P, 5-Chloro-N-cyclohexyl-2-(4-iodo-2-methylphenylamino)benzamide 212630-34-7P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-35-8P, 5-Bromo-N-cyclohexyl-2-(4-iodo-2-methylphenylamino)benzamide 212630-36-9P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-37-0P, N-Cyclohexyl-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-38-1P, [4-Chloro-2-(1H-tetrazol-5-yl)phenyl]-(4-iodo-2-methylphenyl)amine 212630-39-2P, (4-Iodo-2-methylphenyl)-[2-(1H-tetrazol-5-yl)phenyl]amine 212630-40-5P, [4-Nitro-2-(1H-tetrazol-5-yl)-phenyl]-(4-iodo-2-methylphenyl)amine 212630-41-6P, 2-(2-Methyl-4-iodophenylamino)-N-hydroxy-4-fluorobenzamide 212630-42-7P, 5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methylphenylamino)benzamide 212630-43-8P, 2-(4-Bromo-2-methylphenylamino)-4-fluoro-N-hydroxybenzamide 212630-44-9P, 5-Chloro-N-hydroxy-2-(4-iodo-2-methylphenylamino)-N-methylbenzamide 212630-45-0P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(terahydropyran-2-yloxy)benzamide 212630-46-1P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-methoxybenzamide 212630-47-2P, 4-Fluoro-N-hydroxy-2-(4-fluoro-2-methylphenylamino)benzamide 212630-48-3P, 4-Fluoro-N-hydroxy-2-(2-

methylphenylamino)benzamide 212630-49-4P, 4-Fluoro-2-(4-fluoro-2-methylphenylamino)-N-(tetrahydropyran-2-yloxy)benzamide 212630-50-7P, 4-Fluoro-N-hydroxy-2-(4-chloro-2-methylphenylamino)benzamide 212630-51-8P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-phenylmethoxybenzamide 212630-52-9P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-methoxybenzamide 212630-53-0P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-methoxybenzamide 212630-54-1P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-methoxybenzamide 212630-55-2P, 2-(4-Bromo-2-methylphenylamino)-N-ethoxy-3,4-difluorobenzamide 212630-56-3P, 5-Bromo-N-ethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-57-4P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-isopropoxybenzamide 212630-58-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-isopropoxybenzamide 212630-59-6P, 4-Fluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 212630-60-9P, 3,4-Difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 212630-61-0P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(furan-3-ylmethoxy)benzamide 212630-62-1P, 5-Bromo-3,4-difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 212630-63-2P, 5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-64-3P 212630-65-4P 212630-66-5P 212630-67-6P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(1-methyl-2-propyn-1-yloxy)benzamide 212630-68-7P 212630-69-8P 212630-70-1P 212630-71-2P 212630-72-3P 212630-73-4P 212630-74-5P 212630-75-6P 212630-76-7P 212630-77-8P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(3-methyl-5-phenylpent-2-en-4-ynyloxy)benzamide 212630-78-9P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(3-methyl-5-phenylpent-2-en-4-ynyloxy)benzamide 212630-79-0P, N-Ethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-80-3P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-propoxybenzamide 212630-81-4P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-propoxybenzamide 212630-82-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-propoxybenzamide 212630-83-6P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-propoxybenzamide 212630-84-7P

, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-isopropoxybenzamide 212630-85-8P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-isopropoxybenzamide 212630-86-9P, N-Cyclobutyloxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-87-0P, 2-(4-Bromo-2-methylphenylamino)-N-cyclobutyloxy-3,4-difluorobenzamide 212630-88-1P, N-Cyclopentyloxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-89-2P, 2-(4-Bromo-2-methylphenylamino)-N-cyclopentyloxy-3,4-difluorobenzamide 212630-90-5P, N-Cyclopropylmethoxy-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-91-6P, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-92-7P, 2-(4-Bromo-2-methylphenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide 212630-94-9P 212630-96-1P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-phenoxyethoxy)benzamide 212630-98-3P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-phenoxyethoxy)benzamide 212630-99-4P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-phenoxyethoxy)benzamide 212631-00-0P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(thiophen-2-ylmethoxy)benzamide 212631-01-1P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(thiophen-2-ylmethoxy)benzamide 212631-02-2P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(thiophen-2-ylmethoxy)benzamide 212631-03-3P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-methylallyloxy)benzamide 212631-04-4P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-methylallyloxy)benzamide

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)

IT 212631-05-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-

methylallyloxy)benzamide 212631-06-6P, N-(But-2-enyloxy)-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212631-07-7P, N-(But-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212631-08-8P, 2-(4-Bromo-2-methylphenylamino)-N-(but-2-enyloxy)-3,4-difluorobenzamide 212631-09-9P 212631-13-5P 212631-15-7P, N-Cyclopentyloxy-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212631-28-2P 212631-29-3P 212631-30-6P 212631-32-8P 212631-33-9P 212631-34-0P 212631-35-1P 212631-36-2P, 5-Chloro-N-hydroxy-2-(4-iodo-2-methylphenylamino)benzamide 212631-37-3P 212631-38-4P 212631-39-5P 212631-40-8P 212631-41-9P 212631-42-0P 212631-43-1P 212631-44-2P 212631-45-3P 212631-46-4P, 5-Bromo-2-(2-chloro-4-iodophenylamino)-3,4-difluoro-N-hydroxybenzamide 212631-47-5P 212631-48-6P 212631-49-7P 212631-50-0P 212631-51-1P 212631-52-2P 212631-54-4P 212631-55-5P 212631-56-6P 212631-57-7P, 2-(2-Chloro-4-iodophenylamino)-4-fluoro-N-hydroxybenzamide 212631-58-8P 212631-59-9P 212631-60-2P 212631-61-3P, N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-methylphenylamino)benzamide 212631-62-4P 212631-63-5P 212631-64-6P 212631-65-7P 212631-66-8P 212631-67-9P, 5-Bromo-2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide 212631-68-0P 212631-69-1P 212631-70-4P 212631-71-5P 212631-72-6P 212631-73-7P 212631-75-9P 212631-76-0P 212631-77-1P 212631-78-2P, 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-4-fluorobenzamide 212631-79-3P, 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide 212631-80-6P 212631-81-7P 219777-46-5P, N-(3-tert-Butylpropyn-2-yl)oxy-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 219777-60-3P, 2-(2-Methyl-4-iodophenylamino)-N-hydroxy-3,4-difluorobenzamide 219778-04-8P, 2-(2-Chloro-4-iodophenylamino)-N-cyclobutylmethoxy-3,4-difluorobenzamide 219778-52-6P 219794-13-5P 219794-21-5P, 2-(4-Iodo-2-methylphenylamino)-5-nitrothiobenzoic acid S-benzyl ester 277315-06-7P, (3-Hydroxypyrrolidin-1-yl)-[2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]methanone 277315-07-8P, [5-Bromo-2-(4-iodo-2-methylphenylamino)phenyl]-(3-hydroxypyrrolidin-1-yl)-methanone 277315-08-9P, [5-Chloro-2-(4-iodo-2-methylphenylamino)phenyl]-(3-hydroxypyrrolidin-1-yl)-methanone 277315-09-0P, [5-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-(3-hydroxypyrrolidin-1-yl)-methanone 277315-10-3P 277315-12-5P 277335-40-7P 277335-43-0P 278609-85-1P, 2-(4-Iodophenylamino)-N-cyclopropylmethoxy-5-chloro-3,4-difluorobenzamide 278609-99-7P, 2-(4-Iodophenylamino)-5-chloro-3,4-difluorobenzoic acid 278610-42-7P, 2-(2-Chloro-4-iodophenylamino)-5-chloro-3,4-difluorobenzoic acid 278610-51-8P, 5-Chloro-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)

IT 79955-99-0, Stromelysin 1 142805-58-1, MEK protein kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)

IT 352-33-0, 1-Chloro-4-fluorobenzene 1583-58-0, 2,4-Difluorobenzoic acid 6723-30-4, O-(Tetrahydro-2H-pyran-2-yl)-hydroxylamine 176317-02-5, 1-Bromo-2,3,4-trifluorobenzene

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)

IT 13194-68-8P, 2-Amino-5-iodotoluene 57381-34-7P, 5-Chloro-2-fluorobenzonitrile 96515-79-6P, 5-Chloro-2-fluorobenzaldehyde 212631-82-8P, 5-Chloro-2-fluorobenzaldehyde oxime 212631-83-9P,

5-(5-Chloro-2-fluorophenyl)-1H-tetrazole 212631-84-0P 212631-85-1P,  
 5-Bromo-2,3 4-trifluorobenzoic acid 212631-86-2P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK  
 inhibitors by addition of halobenzoic acids to haloanilines and optional  
 reduction or amidation of the acid)

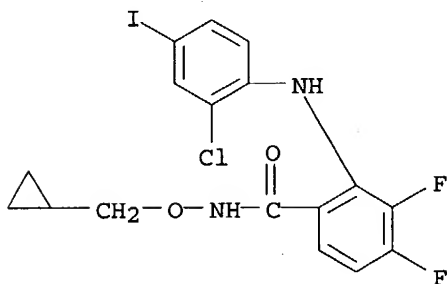
IT 212631-79-3P, 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-  
 3,4-difluorobenzamide

RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
 study, unclassified); SPN (Synthetic preparation); THU (Therapeutic  
 use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK  
 inhibitors by addition of halobenzoic acids to haloanilines and optional  
 reduction or amidation of the acid)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-  
 difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 19 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2000:420948 HCAPLUS

DN 133:73859

ED Entered STN: 23 Jun 2000

TI Preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivatives  
 as MEK inhibitors

IN Gilbertsen, Richard Buell

PA Warner-Lambert Co., USA

SO PCT Int. Appl., 128 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-00

ICS A61K031-196; A61K031-166; A61K031-136; A61K031-41; A61K031-495;  
 A61K031-4453; A61K031-40; A61K031-4465; A61K031-5375; A61K031-381;  
 A61K031-341; A61K031-18; A61P037-06

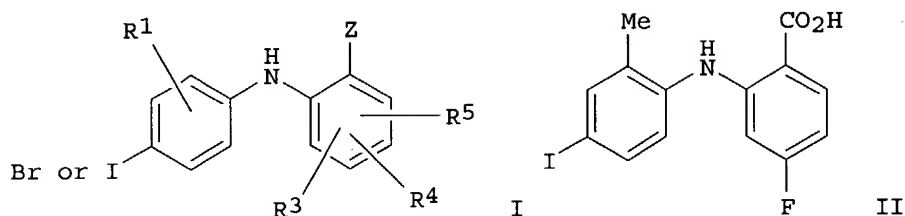
CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)

Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000035435	A1	20000622	WO 1999-US29591	19991214 <--
	W:	AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	CA 2346684	AA	20000622	CA 1999-2346684	19991214 <--

EP 1140046 A1 20011010 EP 1999-966203 19991214 <--  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
 IE, SI, LT, LV, FI, RO  
 TR 200101704 T2 20011121 TR 2001-200101704 19991214 <--  
 JP 2002532414 T2 20021002 JP 2000-587756 19991214 <--  
 ZA 2001003765 A 20020509 ZA 2001-3765 20010509 <--  
 PRAI US 1998-112369P P 19981215 <--  
 WO 1999-US29591 W 19991214 <--  
 OS MARPAT 133:73859  
 GI



AB The title compds. (I) [wherein R1 = H, OH, alkyl, alkoxy, halo, CF3, or CN; R3-R5 = independently H, OH, halo, CF3, alkyl, alkoxy, NO2, CN, or (O or NH)m-(CH2)n-R9, where R9 = H, OH, CO2H, or NR10R11; m = 0 or 1; n = 0-4; R10 and R11 = H, alkyl, or taken together with the N to which they are attached form a 3-10 membered ring; Z = CO2R7, tetrazolyl, CONR6R7, CONHNR10R11, or CH2OR7; R6 and R7 = independently H, (cyclo)alkyl, alkenyl, alkynyl, acyl, (hetero)aryl, or taken together with the N to which they are attached form a 3-10 membered ring, etc.] were prepared by standard or combinatorial synthetic methods involving the addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid. For example, treatment of 2-amino-5-iodotoluene in THF with LDA in THF/heptane/ethenylbenzene solution, followed by addition of 2,4-difluorobenzoic acid in THF afforded II. In a mixed lymphocyte (or leukocyte) reaction (MLR) assay, 2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide (PD 184352) improved histocompatibility and gave IC50 of 186 nM. PD 184352 demonstrated potent immunosuppressive activity by causing almost total inhibition of Con A induced T cell proliferation at the highest dose tested (10.0  $\mu$ M) with IC50 of 340 nM. Thus, I are potent MEK inhibitors with immunosuppressive properties that are useful for preventing and controlling the rejection of transplants in mammals.

ST diphenylamine std combinatorial prepn MEK inhibitor; bromophenylamino iodophenylamino benzamide prepn immunosuppressant; benzamide bromophenylamino iodophenylamino prepn transplant rejection prevention treatment

IT Transplant and Transplantation  
 (graft-vs.-host reaction, treatment; preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)

IT Combinatorial library  
 Immunosuppressants  
 Solid phase synthesis  
 Toxicity  
 (preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)

- IT CD28 (antigen)  
CD3 (antigen)  
Interleukin 2  
Phytohemagglutinins  
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT T cell (lymphocyte)  
(proliferation; preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT Interferons  
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)  
( $\gamma$ ; preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT 212630-42-7P, PD 171984 212630-94-9P, PD 177168 212631-46-4P, PD 184386 212631-57-7P, PD 185848 212631-61-3P, PD 198306 212631-67-9P, PD 184161 212631-78-2P, PD 203311 212631-79-3P, PD 184352 219778-04-8P, PD 185625 219778-52-6P, PD 180841  
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT 212628-43-8P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-46-1P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-48-3P, 5-Chloro-2-(4-iodo-2-methylphenylamino)benzoic acid  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT 212628-44-9P, 3,4,5-Trifluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-45-0P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-47-2P, 5-Chloro-2-(2-chloro-4-iodophenylamino)benzoic acid  
212628-49-4P, Sodium 5-Chloro-2-(4-iodo-2-methylphenylamino)benzoate  
212628-50-7P, 5-Bromo-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-51-8P, 2-(2-Chloro-4-iodophenylamino)-5-nitrobenzoic acid  
212628-52-9P 212628-53-0P, 2-(4-Iodo-2-methylphenylamino)-5-nitrobenzoic acid 212628-54-1P, 2-(2-Fluoro-4-iodophenylamino)-5-nitrobenzoic acid  
212628-55-2P, 2-(4-Bromo-2-methylphenylamino)-4-fluorobenzoic acid  
212628-56-3P, 2-(2-Bromo-4-iodophenylamino)-5-nitrobenzoic acid  
212628-57-4P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluorobenzoic acid  
212628-58-5P, 3-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-59-6P, 3,4-Difluoro-2-(4-iodo-2-methoxyphenylamino)benzoic acid  
212628-60-9P, 4-Chloro-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-61-0P, 2-(4-Iodo-2-methylphenylamino)benzoic acid 212628-62-1P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-63-2P, 5-Iodo-2-(4-iodo-2-methylphenylamino)benzoic acid 212628-65-4P, 2,3,5-Trifluoro-4-(4-iodo-2-methylphenylamino)benzoic acid 212628-67-6P  
212628-69-8P, 2-(4-Iodophenylamino)-5-methoxybenzoic acid 212628-71-2P, 3-Chloro-2-(2-chloro-4-iodophenylamino)benzoic acid 212628-72-3P, 2-Fluoro-6-(4-iodo-2-methylphenylamino)benzoic acid 212628-73-4P  
212628-74-5P, 5-Methyl-2-(4-iodo-2-methylphenylamino)benzoic acid  
212628-75-6P, 2-Chloro-6-(4-iodo-2-methylphenylamino)benzoic acid

212628-76-7P, 2-(4-Iodo-2-methylphenylamino)-4-nitrobenzoic acid  
212628-77-8P, 5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212628-78-9P 212628-79-0P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212628-80-3P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-methylbenzamide 212628-81-4P,  
N-Ethyl-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212628-82-5P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)-N,N-dimethylbenzamide  
212628-83-6P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(1H-tetrazol-5-yl)-  
benzamide 212628-84-7P, 5-Bromo-2-(4-iodo-2-methylphenylamino)benzamide  
212628-85-8P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N,N-  
dimethylbenzamide 212628-86-9P, [[5-Chloro-2-(4-iodo-2-methylphenylamino)benzoyl]amino]acetic acid 212628-87-0P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-propylbenzamide 212628-88-1P,  
5-Bromo-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide  
212628-89-2P, N,N-Diethyl-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide  
212628-90-5P, 4-Fluoro-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]propyl]-2-(4-  
iodo-2-methylphenylamino)benzamide 212628-91-6P, N,N-Diethyl-2-(4-iodo-2-  
methylphenylamino)-5-nitrobenzamide 212628-92-7P, N-Butyl-4-fluoro-2-(4-  
iodo-2-methylphenylamino)benzamide 212628-93-8P, 5-Chloro-N,N-diethyl-2-  
(4-iodo-2-methylphenylamino)benzamide 212628-94-9P, 5-Bromo-2-(4-iodo-2-  
methylphenylamino)-N,N-dimethylbenzamide 212628-95-0P 212628-96-1P,  
[5-Chloro-2-(4-iodo-2-methylphenylamino)phenyl]methanol 212628-97-2P,  
[2-(4-Iodo-2-methylphenylamino)-5-nitrophenyl]methanol 212628-98-3P,  
[5-Bromo-2-(4-iodo-2-methylphenylamino)phenyl]methanol 212628-99-4P,  
5-Bromo-3,4-difluoro-N-(2-hydroxyethyl)-2-(4-iodo-2-  
methylphenylamino)benzamide 212629-00-0P, N-(2,3-Dihydroxypropyl)-3,4-  
difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-01-1P,  
5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-  
ylethyl)benzamide 212629-02-2P, 3,4-Difluoro-N-(2-hydroxyethyl)-2-(4-  
iodo-2-methylphenylamino)benzamide 212629-03-3P, N-(2,3-Dihydroxypropyl)-  
4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-04-4P,  
3,4-Difluoro-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide  
212629-05-5P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-  
pyrrolidin-1-ylethyl)benzamide 212629-06-6P, 5-Bromo-3,4-difluoro-2-(4-  
iodo-2-methylphenylamino)-N-(2-pyridin-4-ylethyl)benzamide 212629-07-7P,  
4-Fluoro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide  
212629-08-8P, 5-Bromo-N-(3-dimethylaminopropyl)-3,4-difluoro-2-(4-iodo-2-  
methylphenylamino)benzamide 212629-09-9P, 5-Bromo-3,4-difluoro-2-(4-iodo-  
2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-10-2P,  
3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-  
ylethyl)benzamide 212629-11-3P, 3,4-Difluoro-2-(4-iodo-2-  
methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-12-4P,  
3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyridin-4-  
ylethyl)benzamide 212629-13-5P, N-(3-Dimethylaminopropyl)-3,4-difluoro-2-  
(4-iodo-2-methylphenylamino)benzamide 212629-14-6P, N-Benzyl-4-fluoro-2-  
(4-iodo-2-methylphenylamino)benzamide 212629-15-7P, 2-(4-Bromo-2-  
methylphenylamino)-3,4-difluoro-N-(2-hydroxyethyl)benzamide  
212629-16-8P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-  
ylethyl)benzamide 212629-17-9P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-  
N-(3-piperidin-1-ylpropyl)benzamide 212629-18-0P, 3,4-Difluoro-2-(4-iodo-  
2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-19-1P,  
4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-thiophen-2-ylethyl)benzamide  
212629-20-4P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-  
ylethyl)benzamide 212629-21-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-  
difluoro-N-(2-morpholin-4-ylethyl)benzamide 212629-22-6P,  
5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-pyridin-4-  
ylmethylbenzamide 212629-23-7P, 3,4-Difluoro-2-(4-iodo-2-  
methylphenylamino)-N-pyridin-4-ylmethylbenzamide 212629-24-8P,  
2-(4-Bromo-2-methylphenylamino)-N-(3-dimethylaminopropyl)-3,4-  
difluorobenzamide 212629-25-9P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-  
N-pyridin-4-ylmethylbenzamide 212629-26-0P, 4-Fluoro-2-(4-iodo-2-  
methylphenylamino)-N-(2-pyridin-4-ylethyl)benzamide 212629-27-1P,  
2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-pyridin-4-

ylethyl)benzamide 212629-28-2P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(3-hydroxypropyl)benzamide 212629-29-3P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-30-6P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-phenethylbenzamide 212629-31-7P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-thiophen-2-ylethyl)benzamide 212629-32-8P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-pyridin-4-ylmethylbenzamide 212629-33-9P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-phenethylbenzamide 212629-34-0P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-piperidin-1-ylethyl)benzamide 212629-35-1P, 5-Chloro-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]-propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-36-2P, 5-Fluoro-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]-propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-37-3P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-pyridin-4-ylmethylbenzamide 212629-38-4P, 5-Bromo-N-[3-[4-(2-hydroxyethyl)piperazin-1-yl]-propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-39-5P, 5-Chloro-N-(2-diethylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-40-8P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-41-9P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-42-0P, 5-Bromo-N-(2-diethylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-43-1P, N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-5-chloro-2-(4-iodo-2-methylphenylamino)benzamide 212629-44-2P, N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-5-bromo-2-(4-iodo-2-methylphenylamino)benzamide 212629-45-3P, 2-(4-Iodo-2-methylphenylamino)-5-nitrobenzoic acid phenethyl ester 212629-46-4P, N-[3-[4-(2-Hydroxyethyl)piperazin-1-yl]-propyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-47-5P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-pyridin-4-ylmethylbenzamide 212629-48-6P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-50-0P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-52-2P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide 212629-54-4P, 5-Chloro-N-(3-dimethylaminopropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-56-6P, N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-58-8P, 5-Chloro-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-60-2P, 5-Chloro-N-[3-(N,N-diethylamino)-2-hydroxypropyl]-2-(4-iodo-2-methylphenylamino)benzamide 212629-62-4P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-piperidin-1-ylethyl)benzamide 212629-64-6P, 5-Bromo-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-66-8P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-68-0P, N-[2-[Bis-(2-hydroxyethyl)amino]ethyl]-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212629-69-1P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-71-5P, 5-Chloro-N-(3-diethylaminopropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-73-7P, 5-Chloro-N-(2-diisopropylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-75-9P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-77-1P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-(2-piperidin-1-ylethyl)benzamide 212629-78-2P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-piperazin-1-ylethyl)benzamide 212629-79-3P, N-(2-Diethylaminoethyl)-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-80-6P, 5-Bromo-N-(3-dimethylaminopropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-81-7P, N-(3-Hydroxypropyl)-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212629-82-8P, 5-Fluoro-N-(3-hydroxypropyl)-2-(4-iodo-2-methylphenylamino)benzamide 212629-83-9P, N-(3-Diethylaminopropyl)-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-84-0P, N-(3-Diethylaminopropyl)-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212629-85-1P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-86-2P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-(3-piperidin-1-ylpropyl)benzamide 212629-87-3P, 5-Bromo-N-(2-diisopropylaminoethyl)-2-(4-iodo-2-methylphenylamino)benzamide

212629-88-4P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-morpholin-4-ylethyl)benzamide 212629-89-5P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(3-piperidin-1-ylpropyl)benzamide 212629-90-8P, N-[3-(N,N-Diethylamino)-2-hydroxypropyl]-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-91-9P 212629-92-0P 212629-93-1P, N-(2-Diisopropylaminoethyl)-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212629-94-2P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)thiobenzoic acid S-phenethyl ester 212629-95-3P, 5-Chloro-2-(4-iodo-2-methylphenylamino)thiobenzoic acid S-phenethyl ester 212629-98-6P 212629-99-7P 212630-00-7P, N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-03-0P, 5-Fluoro-N-(2-hydroxyethyl)-2-(4-iodo-2-methylphenylamino)benzamide 212630-04-1P, N-Benzyloxy-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-05-2P, N-Benzyloxy-5-bromo-2-(4-iodo-2-methylphenylamino)benzamide 212630-06-3P, 2-(4-Iodo-2-methylphenylamino)-5-nitro-N-(4-sulfamoylbenzyl)benzamide 212630-07-4P, N-(2-Hydroxyethyl)-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-08-5P, N-(2-Hydroxyethyl)-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-09-6P, 2-(4-Iodo-2-methylphenylamino)-N-methyl-5-nitro-N-phenylbenzamide 212630-10-9P, 5-Chloro-N-cyclopropyl-2-(4-iodo-2-methylphenylamino)benzamide 212630-11-0P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-methyl-N-phenylbenzamide 212630-12-1P, N-Allyl-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-13-2P, N-Benzyloxy-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-14-3P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(4-sulfamoylbenzyl)benzamide 212630-15-4P, N-Allyl-5-chloro-2-(4-iodo-2-methylphenylamino)benzamide 212630-16-5P, N-Cyclopropyl-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-17-6P, 5-Bromo-N-cyclopropyl-2-(4-iodo-2-methylphenylamino)benzamide 212630-18-7P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-methyl-N-phenylbenzamide 212630-19-8P, 5-Iodo-2-(4-iodo-2-methylphenylamino)-N-(4-sulfamoylbenzyl)benzamide 212630-20-1P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(4-sulfamoylbenzyl)benzamide 212630-21-2P, N-Allyl-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-22-3P, N-Allyl-5-bromo-2-(4-iodo-2-methylphenylamino)benzamide 212630-23-4P, 5-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-24-5P, N-Cyclopropyl-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-25-6P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-methyl-N-phenylbenzamide 212630-26-7P, N-Benzyloxy-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-27-8P, N-Cyclohexyl-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-28-9P, N-Allyl-5-iodo-2-(4-iodo-2-methylphenylamino)benzamide 212630-29-0P, 5-Iodo-2-(4-iodo-2-methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-30-3P, 2-(4-Iodo-2-methylphenylamino)-N-(3-methylbenzyl)-5-nitrobenzamide 212630-31-4P, 5-Iodo-2-(4-iodo-2-methylphenylamino)-N-methyl-N-phenylbenzamide 212630-32-5P, N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-33-6P, 5-Chloro-N-cyclohexyl-2-(4-iodo-2-methylphenylamino)benzamide 212630-34-7P, 5-Bromo-2-(4-iodo-2-methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-35-8P, 5-Bromo-N-cyclohexyl-2-(4-iodo-2-methylphenylamino)benzamide 212630-36-9P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(3-methylbenzyl)benzamide 212630-37-0P, N-Cyclohexyl-2-(4-iodo-2-methylphenylamino)-5-nitrobenzamide 212630-38-1P 212630-39-2P, (4-Iodo-2-methylphenyl)-[2-(1H-tetrazol-5-yl)phenyl]amine 212630-41-6P, PD 170611 212630-43-8P, 2-(4-Bromo-2-methylphenylamino)-4-fluoro-N-hydroxybenzamide 212630-44-9P, 5-Chloro-N-hydroxy-2-(4-iodo-2-methylphenylamino)-N-methylbenzamide 212630-45-0P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-(terahydropyran-2-yloxy)benzamide 212630-46-1P, 5-Chloro-2-(4-iodo-2-methylphenylamino)-N-methoxybenzamide 212630-47-2P, 4-Fluoro-N-hydroxy-2-(4-fluoro-2-methylphenylamino)benzamide 212630-48-3P, 4-Fluoro-N-hydroxy-2-(2-methylphenylamino)benzamide 212630-49-4P, 4-Fluoro-2-(4-fluoro-2-methylphenylamino)-N-(terahydropyran-2-yloxy)benzamide 212630-50-7P, 4-Fluoro-N-hydroxy-2-(4-chloro-2-

methylphenylamino)benzamide 212630-51-8P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-phenylmethoxybenzamide 212630-52-9P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-methoxybenzamide 212630-53-0P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-methoxybenzamide 212630-54-1P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-methoxybenzamide 212630-55-2P, 2-(4-Bromo-2-methylphenylamino)-N-ethoxy-3,4-difluorobenzamide 212630-56-3P, 5-Bromo-N-ethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-57-4P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-isopropoxybenzamide 212630-58-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-isopropoxybenzamide 212630-59-6P, 4-Fluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 212630-60-9P, 3,4-Difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 212630-61-0P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(furan-3-ylmethoxy)benzamide 212630-62-1P, 5-Bromo-3,4-difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methylphenylamino)benzamide 212630-63-2P, 5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-64-3P 212630-65-4P 212630-66-5P 212630-67-6P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(1-methyl-2-propyn-1-yloxy)benzamide 212630-68-7P 212630-69-8P 212630-70-1P 212630-71-2P 212630-72-3P 212630-73-4P 212630-74-5P 212630-75-6P 212630-76-7P 212630-77-8P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(3-methyl-5-phenylpent-2-en-4-ynyloxy)benzamide 212630-78-9P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(3-methyl-5-phenylpent-2-en-4-ynyloxy)benzamide 212630-79-0P, N-Ethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-80-3P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-propoxybenzamide 212630-81-4P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-propoxybenzamide 212630-82-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-propoxybenzamide 212630-83-6P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-propoxybenzamide 212630-84-7P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-isopropoxybenzamide 212630-85-8P, 5-Bromo-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-N-isopropoxybenzamide 212630-86-9P, N-Cyclobutyloxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-87-0P, 2-(4-Bromo-2-methylphenylamino)-N-cyclobutyloxy-3,4-difluorobenzamide 212630-88-1P, N-Cyclopentyloxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-89-2P, 2-(4-Bromo-2-methylphenylamino)-N-cyclopentyloxy-3,4-difluorobenzamide 212630-90-5P, N-Cyclopropylmethoxy-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-91-6P, N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide 212630-92-7P, 2-(4-Bromo-2-methylphenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide 212630-96-1P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-phenoxyethoxy)benzamide 212630-98-3P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-phenoxyethoxy)benzamide 212630-99-4P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-phenoxyethoxy)benzamide 212631-00-0P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(thiophen-2-ylmethoxy)benzamide 212631-01-1P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(thiophen-2-ylmethoxy)benzamide 212631-02-2P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(thiophen-2-ylmethoxy)benzamide 212631-03-3P, 4-Fluoro-2-(4-iodo-2-methylphenylamino)-N-(2-methylallyloxy)benzamide 212631-04-4P, 3,4-Difluoro-2-(4-iodo-2-methylphenylamino)-N-(2-methylallyloxy)benzamide 212631-05-5P, 2-(4-Bromo-2-methylphenylamino)-3,4-difluoro-N-(2-methylallyloxy)benzamide 212631-06-6P, N-(But-2-enyloxy)-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212631-07-7P, N-(But-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methylphenylamino)benzamide

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)

- IT 212631-08-8P, 2-(4-Bromo-2-methylphenylamino)-N-(but-2-enyloxy)-3,4-difluorobenzamide 212631-09-9P 212631-13-5P 212631-15-7P, N-Cyclopentyloxy-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 212631-28-2P 212631-29-3P 212631-33-9P 212631-35-1P 212631-36-2P, 5-Chloro-N-hydroxy-2-(4-iodo-2-methylphenylamino)benzamide 212631-37-3P, 212631-38-4P 212631-39-5P 212631-40-8P 212631-41-9P 212631-42-0P 212631-43-1P 212631-44-2P 212631-45-3P 212631-47-5P 212631-48-6P 212631-49-7P 212631-50-0P 212631-51-1P 212631-52-2P 212631-53-3P 212631-54-4P 212631-55-5P 212631-56-6P 212631-58-8P 212631-59-9P 212631-60-2P 212631-62-4P, PD 298127 212631-63-5P 212631-64-6P 212631-65-7P 212631-66-8P 212631-68-0P 212631-69-1P 212631-70-4P, PD 297189 212631-71-5P 212631-72-6P 212631-73-7P 212631-74-8P 212631-75-9P 212631-76-0P 212631-77-1P 212631-80-6P 212631-81-7P 219777-46-5P, N-(3-tert-Butylpropyn-2-yl)oxy-4-fluoro-2-(4-iodo-2-methylphenylamino)benzamide 219777-60-3P, PD 188563 219794-13-5P 219794-21-5P, 2-(4-Iodo-2-methylphenylamino)-5-nitrothiobenzoic acid S-benzyl ester 277315-06-7P, (3-Hydroxypyrrolidin-1-yl)-[2-(4-iodo-2-methylphenylamino)-5-nitrophenyl]methanone 277315-07-8P, [5-Bromo-2-(4-iodo-2-methylphenylamino)phenyl]-(3-hydroxypyrrolidin-1-yl)-methanone 277315-08-9P, [5-Chloro-2-(4-iodo-2-methylphenylamino)phenyl]-(3-hydroxypyrrolidin-1-yl)-methanone 277315-09-0P, [5-Fluoro-2-(4-iodo-2-methylphenylamino)phenyl]-(3-hydroxypyrrolidin-1-yl)-methanone 277315-10-3P 277315-12-5P 277335-43-0P 278609-85-1P, PD 297190 278609-99-7P, PD 296711 278610-42-7P, PD 296770 278610-51-8P, PD 296767
- RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT 11028-71-0, Concanavalin A 142805-58-1
- RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT 352-33-0, 1-Chloro-4-fluorobenzene 1583-58-0, 2,4-Difluorobenzoic acid 6723-30-4, O-(Tetrahydro-2H-pyran-2-yl)-hydroxylamine 176317-02-5, 1-Bromo-2,3,4-trifluorobenzene
- RL: RCT (Reactant); RACT (Reactant or reagent)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- IT 13194-68-8P, 2-Amino-5-iodotoluene 57381-34-7P, 5-Chloro-2-fluorobenzonitrile 96515-79-6P, 5-Chloro-2-fluorobenzaldehyde 212631-82-8P, 5-Chloro-2-fluorobenzaldehyde oxime 212631-83-9P, 5-(5-Chloro-2-fluorophenyl)-1H-tetrazole 212631-84-0P 212631-85-1P, 5-Bromo-2,3,4-trifluorobenzoic acid 212631-86-2P
- RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)
- RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
- RE
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  - (6) Warner Lambert Co; EP 0316630 A 1989 HCAPLUS
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(8) Warner Lambert Co; WO 9631206 A 1996 HCAPLUS

(9) Williams, J; WO 9601111 A 1996 HCAPLUS

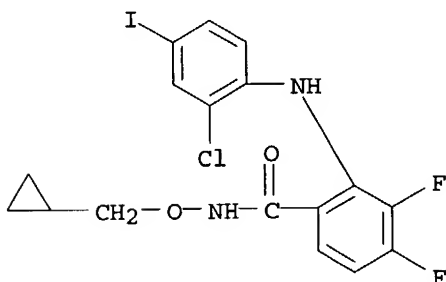
IT 212631-79-3P, PD 184352

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivs. as MEK inhibitors by addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



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ED Entered STN: 21 Jul 1999

TI Blockade of the MAP kinase pathway suppresses growth of colon tumors in vivo

AU Sebolt-Leopold, Judith S.; Dudley, David T.; Herrera, Roman; Van Becelaere, Keri; Wiland, Amy; Gowan, Richard C.; Tecle, Haile; Barrett, Stephen D.; Bridges, Alexander; Przybranowski, Sally; Leopold, W. R.; Saltiel, Alan R.

CS Department of Cell Biology, Division of Warner-Lambert, Parke-Davis Pharmaceutical Research, Ann Arbor, MI, 48105, USA

SO Nature Medicine (New York) (1999), 5(7), 810-816

CODEN: NAMEFI; ISSN: 1078-8956

PB Nature America

DT Journal

LA English

CC 1-6 (Pharmacology)

AB The mitogen-activated protein kinase pathway is thought to be essential in cellular growth and differentiation. Here we report the discovery of PD 184352 (2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide), a highly potent and selective inhibitor of the upstream kinase MEK, that is orally active. Tumor growth was inhibited as much as 80% in mice with colon carcinomas of both mouse and human origin after treatment with this inhibitor. Efficacy was achieved with a wide range of doses with no signs of toxicity, and correlated with a reduction in the levels of activated mitogen-activated protein kinase in excised tumors. These data indicate that MEK inhibitors represent a promising, noncytotoxic approach to the clin. management of colon cancer.

ST MAP kinase blockade colon tumor inhibition; PD184352 MEK inhibitor colon tumor treatment

IT Intestine, neoplasm

Intestine, neoplasm

(colon, inhibitors; blockade of MAP kinase pathway suppresses growth of colon tumors in vivo)

IT Antitumor agents  
(colon; blockade of MAP kinase pathway suppresses growth of colon tumors in vivo)

IT 212631-79-3, PD 184352  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(blockade of MAP kinase pathway suppresses growth of colon tumors in vivo)

IT 142805-58-1, Protein kinase MEK  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(inhibitors; MEK inhibitors represent a promising, noncytotoxic approach to the clin. management of colon cancer)

RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD

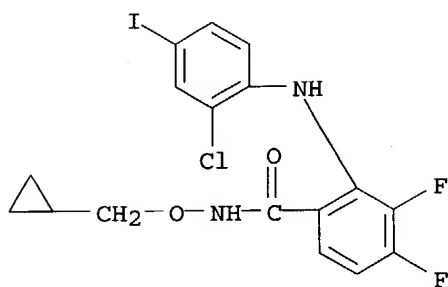
RE

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IT 212631-79-3, PD 184352  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(blockade of MAP kinase pathway suppresses growth of colon tumors in vivo)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 21 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1999:48698 HCAPLUS

DN 130:124900

ED Entered STN: 25 Jan 1999

TI Preparation of 4-bromo or 4-iodo phenylamino benzhydroxamic acid derivatives as MEK inhibitors

IN Barrett, Stephen Douglas; Bridges, Alexander James; Doherty, Annette Marian; Dudley, David Thomas; Saltiel, Alan Robert; Tecle, Haile

PA Warner-Lambert Company, USA

SO PCT Int. Appl., 65 pp.

CODEN: PIXXD2

DT Patent

LA English

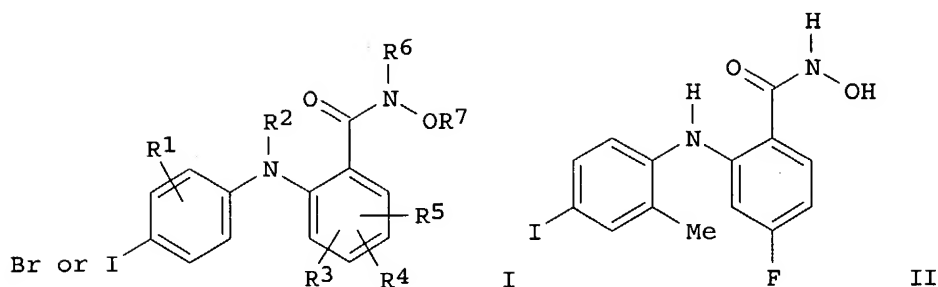
IC ICM C07C259-10

ICS C07D295-08; C07D309-12; A61K031-165

CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)  
Section cross-reference(s): 1, 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9901426	A1	19990114	WO 1998-US13106	19980624 <--
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	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9882627	A1	19990125	AU 1998-82627	19980624 <--
	AU 757046	B2	20030130		
	EP 993439	A1	20000419	EP 1998-932830	19980624 <--
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	NZ 501276	A	20001027	NZ 1998-501276	19980624 <--
	JP 2002511092	T2	20020409	JP 1999-507228	19980624 <--
	TW 396149	B	20000701	TW 1998-87110252	19980625 <--
	ZA 9805728	A	19990127	ZA 1998-5728	19980630 <--
	MX 9910649	A	20000430	MX 1999-10649	19991118 <--
	NO 9906491	A	19991229	NO 1999-6491	19991227 <--
	US 2003078428	A1	20030424	US 2002-163890	20020604 <--
PRAI	US 1997-51440P	P	19970701		<--
	WO 1998-US13106	W	19980624		<--
	US 2000-462239	B1	20000104		<--
OS	MARPAT 130:124900				
GI					



- AB The title compds. [I; R1 = H, OH, C1-8 alkyl, etc.; R2 = H; R3-R5 = H, OH, halo, etc.; R6 = H, C1-8 alkyl, aryl, etc.; R7 = H, C1-8 alkyl, C2-8 alkenyl, etc.], which are potent inhibitors of MEK and, as such, are effective in treating cancer and other proliferative diseases such as psoriasis, restenosis, autoimmune disease, or atherosclerosis, and also stroke, heart failure, hepatomegaly, cardiomegaly, diabetes, Alzheimer's disease, and cystic fibrosis, were prepared and formulated. Thus, treatment of 2-amino-5-iodotoluene in THF with LDA in THF/heptane/ethylbenzene solution followed by addition of 2,4-difluorobenzoic acid in THF, and reaction of the resulting 4-fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid with O-(tetrahydro-2H-pyran-2-yl)hydroxylamine in the presence of diisopropylethylamine and PyBOP in THF/CH<sub>2</sub>Cl<sub>2</sub>, and treatment of the intermediate with ethanolic HCl afforded II which showed IC<sub>50</sub> of 0.007  $\mu$ M against MEK in vitro.
- ST MEK inhibitor bromophenylaminobenzhydroxamic iodophenylaminobenzhydroxamic acid prepn formulation; antiproliferative bromophenylaminobenzhydroxamic iodophenylaminobenzhydroxamic acid prepn formulation; psoriasis bromophenylaminobenzhydroxamic iodophenylaminobenzhydroxamic acid prepn formulation; restenosis bromophenylaminobenzhydroxamic iodophenylaminobenzhydroxamic acid prepn formulation; autoimmune disease bromophenylaminobenzhydroxamic iodophenylaminobenzhydroxamic acid prepn; antiatherosclerotic bromophenylaminobenzhydroxamic iodophenylaminobenzhydroxamic acid prepn formulation; antitumor bromophenylaminobenzhydroxamic iodophenylaminobenzhydroxamic acid prepn formulation; stroke bromophenylaminobenzhydroxamic iodophenylaminobenzhydroxamic acid prepn formulation; heart failure bromophenylaminobenzhydroxamic iodophenylaminobenzhydroxamic acid prepn; hepatomegaly bromophenylaminobenzhydroxamic iodophenylaminobenzhydroxamic acid prepn formulation; antidiabetic bromophenylaminobenzhydroxamic iodophenylaminobenzhydroxamic acid prepn formulation; Alzheimer's disease bromophenylaminobenzhydroxamic iodophenylaminobenzhydroxamic acid prepn; cystic fibrosis bromophenylaminobenzhydroxamic iodophenylaminobenzhydroxamic acid prepn; cardiomegaly bromophenylaminobenzhydroxamic iodophenylaminobenzhydroxamic acid prepn formulation
- IT Antiarteriosclerotics  
(antiatherosclerotics; preparation of 4-bromo or 4-iodo phenylamino benzhydroxamic acid derivs. as MEK inhibitors)
- IT Heart, disease  
(failure, treatment of; preparation of 4-bromo or 4-iodo phenylamino benzhydroxamic acid derivs. as MEK inhibitors)
- IT Liver, disease  
(hepatomegaly, treatment of; preparation of 4-bromo or 4-iodo phenylamino benzhydroxamic acid derivs. as MEK inhibitors)
- IT Antidiabetic agents  
Antitumor agents  
Cytotoxic agents  
(preparation of 4-bromo or 4-iodo phenylamino benzhydroxamic acid derivs. as MEK inhibitors)

IT Proliferation inhibition  
(proliferation inhibitors; preparation of 4-bromo or 4-iodo phenylamino benzhydroxamic acid derivs. as MEK inhibitors)

IT Artery, disease  
(restenosis, treatment of; preparation of 4-bromo or 4-iodo phenylamino benzhydroxamic acid derivs. as MEK inhibitors)

IT Brain, disease  
(stroke, treatment of; preparation of 4-bromo or 4-iodo phenylamino benzhydroxamic acid derivs. as MEK inhibitors)

IT Alzheimer's disease  
Autoimmune disease  
Cystic fibrosis  
Psoriasis  
(treatment of; preparation of 4-bromo or 4-iodo phenylamino benzhydroxamic acid derivs. as MEK inhibitors)

IT 212630-41-6P 212630-42-7P 212630-43-8P 212630-44-9P 212630-45-0P  
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219778-43-5P 219778-48-0P 219778-52-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of 4-bromo or 4-iodo phenylamino benzhydroxamic acid derivs. as MEK inhibitors)

IT 142805-58-1, Mek  
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)  
(preparation of 4-bromo or 4-iodo phenylamino benzhydroxamic acid derivs. as MEK inhibitors)

IT 1583-58-0, 2,4-Difluorobenzoic acid 13194-68-8, 2-Amino-5-iodotoluene  
176317-02-5, 1-Bromo-2,3,4-trifluorobenzene  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(preparation of 4-bromo or 4-iodo phenylamino benzhydroxamic acid derivs. as MEK inhibitors)

IT 212628-43-8P 212628-46-1P 212631-85-1P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(preparation of 4-bromo or 4-iodo phenylamino benzhydroxamic acid derivs. as

MEK inhibitors)

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Bridges, A; US 5525625 A 1996 HCAPLUS

(2) Warner Lambert; WO 9837881 A 1998 HCAPLUS

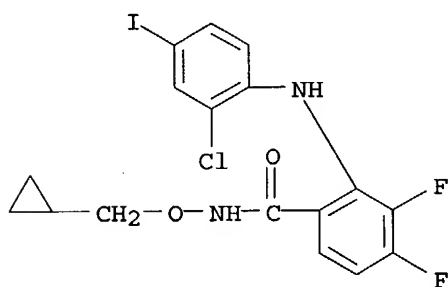
IT 212631-79-3P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 4-bromo or 4-iodo phenylamino benzhydroxamic acid derivs. as MEK inhibitors)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



L112 ANSWER 22 OF 22 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1998:603241 HCAPLUS

DN 129:230537

ED Entered STN: 23 Sep 1998

TI Preparation of 2-phenylaminobenzoic acids and its amides as MEK inhibitors for treating or preventing septic shock

IN Bridges, Alexander James

PA Warner Lambert Co., USA

SO PCT Int. Appl., 110 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-195

ICS A61K031-165; A61K031-135; A61K031-41; A61K031-495; A61K031-445;

A61K031-40; A61K031-44; A61K031-535; A61K031-38; A61K031-34;

A61K031-18

CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)

Section cross-reference(s): 1

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9837881	A1	19980903	WO 1997-US23389	19971217 <--
W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9856103	A1	19980918	AU 1998-56103	19971217 <--
ZA 9801578	A	19980902	ZA 1998-1578	19980225 <--
US 6251943	B1	20010626	US 1999-355680	19990802 <--
PRAI US 1997-39270P	P	19970228	<--	
US 1997-56157P	P	19970819	<--	

WO 1997-US23389 W 19971217 <--  
OS MARPAT 129:230537  
GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The title compds. [I and II; R1 = H, OH, C1-8 alkyl, etc.; R2 = H; R3-R5 = H, OH, halo, etc.; Z = CO2R7, tetrazolyl, CONR6R7, etc.; R6, R7 = H, C1-8 alkyl, C2-8 alkenyl, etc.; R8 = H, C1-8 alkyl, aryl, etc.; R9 = H, C1-8 alkyl, C2-8 alkenyl, etc.], useful in treating or preventing septic shock, were prepared Thus, treatment of 2-amino-5-iodotoluene in THF with LDA/THF/heptane/ethenylbenzene followed by addition 2,4-difluorobenzoic acid afforded 47% III which showed IC50 of 0.019  $\mu$ M against MEK in vitro.

ST MEK inhibitor phenylaminobenzoic acid phenylaminobenzamide prepn; septic shock phenylaminobenzoic acid phenylaminobenzamide prepn

IT Shock (circulatory collapse)  
(septic; preparation of 2-phenylaminobenzoic acids and its amides as MEK inhibitors for treating or preventing septic shock)

IT 212628-48-3P  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(preparation of 2-phenylaminobenzoic acids and its amides as MEK inhibitors for treating or preventing septic shock)

IT

167869-21-8P	212628-43-8P	212628-44-9P	212628-45-0P	212628-46-1P
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212630-38-1P	212630-39-2P	212630-40-5P	212630-41-6P	212630-42-7P
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212630-58-5P	212630-59-6P	212630-60-9P	212630-61-0P	212630-62-1P
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212630-94-9P	212630-96-1P	212630-98-3P	212630-99-4P	

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-phenylaminobenzoic acids and its amides as MEK inhibitors for treating or preventing septic shock)

IT	212631-00-0P	212631-01-1P	212631-02-2P	212631-03-3P	212631-04-4P
	212631-05-5P	212631-06-6P	212631-07-7P	212631-08-8P	212631-09-9P
	212631-10-2P	212631-13-5P	212631-15-7P	212631-25-9P	212631-28-2P
	212631-29-3P	212631-30-6P	212631-31-7P	212631-32-8P	212631-33-9P
	212631-34-0P	212631-35-1P	212631-36-2P	212631-37-3P	212631-38-4P
	212631-39-5P	212631-40-8P	212631-41-9P	212631-42-0P	212631-43-1P
	212631-44-2P	212631-45-3P	212631-46-4P	212631-47-5P	212631-48-6P
	212631-49-7P	212631-50-0P	212631-51-1P	212631-52-2P	212631-53-3P
	212631-54-4P	212631-55-5P	212631-56-6P	212631-57-7P	212631-58-8P
	212631-59-9P	212631-60-2P	212631-61-3P	212631-62-4P	212631-63-5P
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	212631-69-1P	212631-70-4P	212631-71-5P	212631-72-6P	212631-73-7P
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	212631-79-3P	212631-80-6P	212631-81-7P		

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-phenylaminobenzoic acids and its amides as MEK inhibitors for treating or preventing septic shock)

IT 146702-84-3, MEK kinase

RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)

(preparation of 2-phenylaminobenzoic acids and its amides as MEK inhibitors for treating or preventing septic shock)

IT 352-33-0, 1-Chloro-4-fluorobenzene 1583-58-0, 2,4-Difluorobenzoic acid  
6723-30-4 13194-68-8, 2-Amino-5-iodotoluene 176317-02-5,  
1-Bromo-2,3,4-trifluorobenzene

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of 2-phenylaminobenzoic acids and its amides as MEK inhibitors for treating or preventing septic shock)

IT	57381-34-7P	96515-79-6P	212631-82-8P	212631-83-9P	212631-84-0P
	212631-85-1P	212631-86-2P			

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

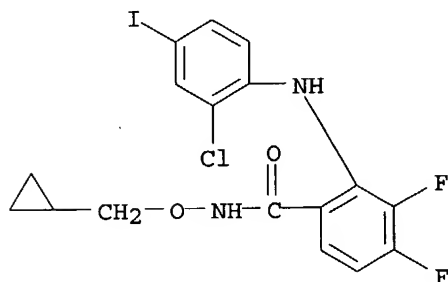
(preparation of 2-phenylaminobenzoic acids and its amides as MEK inhibitors for treating or preventing septic shock)

RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Bekemeier, H; AGENTS ACTIONS SUPPL 1982, P17 HCAPLUS
- (2) Berner, N; JOURNAL OF MEDICINAL CHEMISTRY 1970, V13(3), P552 HCAPLUS
- (3) Derijard, B; WO 9636642 A 1996 HCAPLUS
- (4) Dudley, D; PROC NATL ACAD SCI 1995, V92(17), P7686 HCAPLUS
- (5) Gaidukevich, A; KHIM-FARM ZH 1985, V19(3), P165 HCAPLUS
- (6) Geppert, T; MOLECULAR MEDICINE 1994, V1(1), P93 HCAPLUS
- (7) Ramanujam, P; PLANTA MEDICA 1974, V25(1), P43 HCAPLUS
- (8) Shul'Ga, I; FARM ZH 1972, V27(3), P84 HCAPLUS

(9) Shul'Ga, T; FARM ZH 1988, V1, P42 HCAPLUS  
 (10) Signal Pharm Inc; WO 9722704 A 1997 HCAPLUS  
 (11) van der Bruggen, J; EUROPEAN JOURNAL OF CLINICAL INVESTIGATION 1997, V27(S1), PA19  
 (12) Warner Lambert Co; WO 9622985 A 1996 HCAPLUS  
 IT 212631-79-3P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of 2-phenylaminobenzoic acids and its amides as MEK inhibitors for treating or preventing septic shock)  
 RN 212631-79-3 HCAPLUS  
 CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro- (9CI) (CA INDEX NAME)



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L113 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN  
 AN 2002:171837 HCAPLUS  
 DN 136:232111  
 ED Entered STN: 08 Mar 2002  
 TI Process for making N-arylanthranilic acids and their derivatives  
 IN Chen, Michael Huai Gu; Davis, Edward Mark; Magano, Javier; Nanninga, Thomas Norman; Winkle, Derick Dale  
 PA Warner-Lambert Company, USA  
 SO PCT Int. Appl., 149 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 IC ICM C07C227-08  
 ICS C07C231-12; C07C221-00; C07C253-30; C07C209-04; C07C231-02; C07C067-08  
 CC 25-17 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)  
 FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018319	A1	20020307	WO 2001-US22948	20010720 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001077044	A5	20020313	AU 2001-77044	20010720 <--
EP 1313694	A1	20030528	EP 2001-954824	20010720 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

BR 2001013520 A 20030624 BR 2001-13520 20010720 <--  
JP 2004507518 T2 20040311 JP 2002-523437 20010720 <--  
US 2004039208 A1 20040226 US 2003-344294 20030207  
NO 2003000844 A 20030225 NO 2003-844 20030224 <--  
PRAI US 2000-228206P P 20000825 <--  
WO 2001-US22948 W 20010720  
OS CASREACT 136:232111; MARPAT 136:232111  
AB N-arylanthranilic acids, their esters, amides, and hydroxamic esters are prepared by coupling 1 equivalent of an aniline derivative with 1 equivalent of an aromatic carboxylic acid carrying a leaving group, such as halo, alkyl- or arylsulfonyloxy, or phosphate, in presence of .apprx. 10 equivalent base. Thus, 2,3,4-F3C6H2CO2H was coupled with 2,4-Cl(I)C6H3NH2 in presence of LiN(CHMe2)2 in THF. The base was added at intervals at -20° with warming to room temp between addns. and the yield of 3,4-F2C6H3NHC6H3(I)Cl-4,2 was 78%. This compound was converted to the acid chloride and treated with cyclopropylmethoxyamine hydrochloride to give the N-cyclopropylmethoxyamide. The process is suitable for industrial production  
ST arylanthranilic acid amide prepn manuf  
IT Coupling reaction  
(process for making N-arylanthranilic acids and their derivs.)  
IT 212628-44-9P 219796-77-7P 303175-44-2P  
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(process for making N-arylanthranilic acids and their derivs.)  
IT 644-62-2P 13625-57-5P 17626-44-7P, 2-Diphenylaminobenzoic acid  
72990-98-8P 73323-82-7P 212628-46-1P 212631-61-3P 212631-78-2P  
212631-79-3P 313674-97-4P 313675-05-7P 391211-97-5P  
402955-44-6P 402955-45-7P  
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)  
(process for making N-arylanthranilic acids and their derivs.)  
IT 60-29-7, Diethyl ether, uses 75-05-8, Acetonitrile, uses 77-76-9, 2,2-Dimethoxypropane 109-99-9, Tetrahydrofuran, uses 123-91-1, Dioxane, uses 629-14-1, 1,2-Diethoxyethane 1634-04-4, Methyl tert-butyl ether 7778-85-0, 1,2-Dimethoxypropane  
RL: NUU (Other use, unclassified); USES (Uses)  
(process for making N-arylanthranilic acids and their derivs.)  
IT 100-61-8, N-Methylaniline, reactions 122-39-4, Diphenylamine, reactions 445-29-4, 2-Fluorobenzoic acid 496-15-1, Indoline 1201-31-6, 2,3,4,5-Tetrafluorobenzoic acid 1583-58-0, 2,4-Difluorobenzoic acid 13194-68-8, 4-Iodo-2-methylaniline 29632-74-4, 2-Fluoro-4-iodoaniline 42016-93-3, 2-Chloro-4-iodoaniline 61079-72-9, 2,3,4-Trifluorobenzoic acid 64063-37-2, 2,6-Dichloro-3-methylaniline 74124-04-2, Cyclopropylmethoxyamine hydrochloride 104799-67-9 104800-02-4 402955-41-3 402955-42-4 402955-43-5  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(process for making N-arylanthranilic acids and their derivs.)  
IT 109-02-4, N-Methylmorpholine 141-52-6, Sodium ethoxide 530-62-1 865-47-4 1070-89-9, Sodium bis(trimethylsilyl)amide 2414-98-4, Magnesium ethoxide 4039-32-1, Lithium bis(trimethylsilyl)amide 4111-54-0, Lithium diisopropylamide 7580-67-8, Lithium hydride 7646-69-7, Sodium hydride 7693-26-7, Potassium hydride 7782-89-0, Lithium amide 7782-92-5, Sodium amide 7789-78-8, Calcium hydride 17242-52-3, Potassium amide 40949-94-8, Potassium bis(trimethylsilyl)amide 56602-33-6, BOP hexafluorophosphate  
RL: RGT (Reagent); RACT (Reactant or reagent)  
(process for making N-arylanthranilic acids and their derivs.)  
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD  
RE  
(1) Douglas, B; WO 0041994 A 2000 HCAPLUS

- (2) James, B; WO 9837881 A 1998 HCAPLUS  
(3) Marian, D; WO 9901421 A 1999 HCAPLUS  
(4) Marian, D; WO 9901426 A 1999 HCAPLUS  
(5) Parke Davis & Co; GB 935405 A 1963  
(6) Warner Lambert Co; WO 0064856 A 2000 HCAPLUS

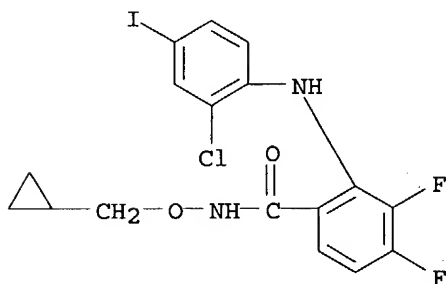
IT 212631-79-3P

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP  
(Preparation)

(process for making N-arylanthranilic acids and their derivs.)

RN 212631-79-3 HCAPLUS

CN Benzamide, 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-  
difluoro- (9CI) (CA INDEX NAME)



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